IN VIVO
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BY IN VIVO’S
BIOPHARMA, MEDTECH AND DIAGNOSTICS TEAMS

2015 & 2016 KEY EVENTS & TRENDS
Pharmaceuticals’ Love Affair With Dealmaking: No End In Sight

Peter Charlish

The pace of pharma dealmaking continued unabated in 2015, climaxing with Pfizer’s agreed $160 billion merger with Allergan. Conditions are right for this situation to persist, at least for the foreseeable future.

Value-Based Medtech Rides The Money-Go-Round Into 2016

Ashley Yeo

The M&A bonanza for companies in the medtech sector continued into 2015 and there is no end in sight in 2016 as manufacturers seek to augment and fine-tune portfolios to meet the new demands of payers and providers. Longer term, there are signs of a change in the top global medtech rankings.

Diagnostics In 2015: Past Trends Coalesce, New Roads Open

Mark Ratner

The introduction of Apple’s ResearchKit is our top story of the year. Mobile apps and the increasing ability to take measurements of vital signs, gather information on habits and collect other phenotypic measures is rapidly changing thinking about clinical trials design.

TG Therapeutics Builds A Business Model For Today

Michael Goodman

The speed with which TG Therapeutics burst on the scene, along with the impressive potency and safety of its novel combinations of cancer drugs, has perhaps blinded observers to the unique business model that has carried it this far.

Navigating Patent Minefields In Emerging Asian Medtech Markets

Gabriela Coman

To be successful in Emerging Asian Markets, medical device companies need superior product and patent protection for both the device and related methods of use, bearing in mind the ease with which devices can be copied by competitors.
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Immunotherapy was prominent in some of the biggest alliances of 2015, with oncology once again being the most partnered therapeutic area, and the largest focus of companies raising venture funding or going public. The year also featured the biggest M&A in biopharma history in Pfizer’s $160 billion takeover of Allergan, motivated by corporate tax reduction. In addition, there was major consolidation within health services industries including PBMs.

We focus here on the dealmakers, showing which companies dominated the landscape in terms of deal volume and value, as well as the therapeutic categories that grabbed the most attention.

**Exhibit 1**

**2015’s Top Five Most Active Pharmaceutical In-Licensers**

*Listed below each company are its top deals by potential deal value ($m)*

*Includes deals by parent companies and their subsidiaries*

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>2015 DEAL VOLUME: 18</th>
<th>2014 DEAL VOLUME: 15</th>
<th>% CHANGE: 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson &amp; Johnson</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>November</td>
<td>Hanmi Pharmaceutical</td>
<td>Phase I HM12525A, a long-acting glucagon-like peptide-1 (GLP-1)/glucagon (GCG) analog</td>
<td>915</td>
</tr>
<tr>
<td>January</td>
<td>Ionis Pharmaceuticals</td>
<td>Up to three antisense therapeutics for autoimmune disorders of the GI tract</td>
<td>835</td>
</tr>
<tr>
<td>December</td>
<td>Bavarian Nordic</td>
<td>MVA-BN (Modified Vaccinia Ankara - Bavarian Nordic) technology to develop a heterologous prime-boost vaccine for HPV</td>
<td>171</td>
</tr>
</tbody>
</table>

**Astrazeneca**

<table>
<thead>
<tr>
<th>2015 DEAL VOLUME: 16</th>
<th>2014 DEAL VOLUME: 6</th>
<th>% CHANGE: 167%</th>
</tr>
</thead>
<tbody>
<tr>
<td>April</td>
<td>Innate Pharma</td>
<td>Phase II NKG2A inhibitor IPH2201 as monotherapy or combination with AZ/MedImmune’s MEDI4736 (durvalumab)</td>
</tr>
<tr>
<td>August</td>
<td>Inovio Pharmaceuticals</td>
<td>Phase I/II cancer immunotherapy INO3112</td>
</tr>
<tr>
<td>February</td>
<td>Allergan (formerly Actavis)</td>
<td>Branded respiratory drug portfolio</td>
</tr>
</tbody>
</table>

**Sanofi**

<table>
<thead>
<tr>
<th>2015 DEAL VOLUME: 15</th>
<th>2014 DEAL VOLUME: 9</th>
<th>% CHANGE: 67%</th>
</tr>
</thead>
<tbody>
<tr>
<td>November</td>
<td>Hanmi Pharmaceutical</td>
<td>Quantum Project: Phase II efpeglenatide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist for Type II diabetes and obesity; a Phase I weekly insulin (HM12470); and a preclinical GLP-1/insulin combination</td>
</tr>
<tr>
<td>July</td>
<td>Regeneron Pharmaceuticals</td>
<td>Phase I PD-1 inhibitor and preclinical programs, potentially targeting LAG3, GITR, and PD-L1</td>
</tr>
<tr>
<td>November</td>
<td>Lexicon Pharmaceuticals</td>
<td>Phase III sotagliflozin (LX4211) for Type I and II diabetes</td>
</tr>
</tbody>
</table>
### Biopharmaceutical Dealmaking

#### Roche

<table>
<thead>
<tr>
<th>Date</th>
<th>License</th>
<th>Subject of License</th>
<th>Potential Deal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>December</td>
<td>SQZ Biotechnologies</td>
<td><em>CellSqueeze</em> technology to modify B-cells and trigger an immune-mounted cascade to treat several types of cancer</td>
<td>500</td>
</tr>
<tr>
<td>December</td>
<td>Pieris Pharmaceuticals</td>
<td><em>Anticalin</em> programs against an undisclosed cancer target</td>
<td>416</td>
</tr>
<tr>
<td>October</td>
<td>Arvinas</td>
<td><em>PROTAC</em> (proteolysis-targeting chimera) drug candidates</td>
<td>300</td>
</tr>
</tbody>
</table>

#### Novartis

<table>
<thead>
<tr>
<th>Date</th>
<th>License</th>
<th>Subject of License</th>
<th>Potential Deal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>August</td>
<td>GlaxoSmithKline</td>
<td>Rights to the Phase II CD20 antagonist ofatumumab in the autoimmune disease field including multiple sclerosis</td>
<td>1,034</td>
</tr>
<tr>
<td>March</td>
<td>Aduro Biotech</td>
<td>Preclinical cyclic dinucleotide (CDN) program</td>
<td>750</td>
</tr>
<tr>
<td>October</td>
<td>Xoma</td>
<td>Preclinical anti-transforming growth factor-beta (TGFβ) antibody XOMA089 for cancer</td>
<td>517</td>
</tr>
</tbody>
</table>

*Potential Deal Value is the sum of up-front fees plus pre-commercialization money.

**Source:** Strategic Transactions

---

**Exhibit 2**

**Top Ten Biopharma Acquisitions of 2015**

<table>
<thead>
<tr>
<th>Date</th>
<th>Acquirer</th>
<th>Acquired</th>
<th>Primary Asset(s) Gained Through Deal</th>
<th>Potential Deal Value (SM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>November</td>
<td>Pfizer</td>
<td>Allergan</td>
<td><em>Botox</em> (onabotulinumtoxinA), <em>Restasis</em> (cyclosporine); other specialty products</td>
<td>160,000</td>
</tr>
<tr>
<td>July</td>
<td>Anthem</td>
<td>Cigna</td>
<td>Medical, dental, disability, life, and accident insurance offerings and related products and health services</td>
<td>48,267</td>
</tr>
<tr>
<td>July</td>
<td>Teva</td>
<td>Allergan Generics</td>
<td>Allergan PLC's generic business, excluding OTC eye care; puts Teva in top three position in over 40 international generic market</td>
<td>40,500</td>
</tr>
<tr>
<td>July</td>
<td>Aetna</td>
<td>Humana</td>
<td>Creates the fourth-largest PBM</td>
<td>34,775</td>
</tr>
<tr>
<td>March</td>
<td>AbbVie</td>
<td>Pharmacycics</td>
<td>Hematological cancer drug <em>Imbruvica</em> (ibrutinib), a Bruton's tyrosine kinase (BTK) inhibitor</td>
<td>19,859</td>
</tr>
<tr>
<td>October</td>
<td>Walgreens Boots</td>
<td>Rite Aid</td>
<td>Third-largest US retail drugstore</td>
<td>17,200</td>
</tr>
<tr>
<td>February</td>
<td>Pfizer</td>
<td>Hospira</td>
<td>Acute care and oncology injectables, and biosimilars</td>
<td>17,119</td>
</tr>
<tr>
<td>March</td>
<td>OptumRx</td>
<td>Catamaran</td>
<td>PBM, including retail pharmacy network management, mail service pharmacy, pharmacy claims management, and specialty pharmacy services</td>
<td>12,793</td>
</tr>
<tr>
<td>May</td>
<td>CVS</td>
<td>Omnicare</td>
<td>Pharmacy services to US long-term care and assisted living facilities</td>
<td>11,795</td>
</tr>
<tr>
<td>February</td>
<td>Valeant</td>
<td>Salix</td>
<td>GI drugs, including <em>Xifaxan</em> (rifamixin) for hepatic encephalopathy and travelers’ diarrhea</td>
<td>11,115</td>
</tr>
</tbody>
</table>

*Includes the up-front fee plus potential earn-out payments.

**Source:** Strategic Transactions
### Exhibit 3
2015's Top Dealmakers: Cancer, Neurology And Infectious Disease*

<table>
<thead>
<tr>
<th>Medical Area</th>
<th>Alliances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>201</td>
</tr>
<tr>
<td>Neurology</td>
<td>74</td>
</tr>
<tr>
<td>Infectious &amp; Viral Diseases</td>
<td>54</td>
</tr>
<tr>
<td>Metabolic Disorders</td>
<td>51</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>47</td>
</tr>
<tr>
<td>Immune Disorders</td>
<td>41</td>
</tr>
<tr>
<td>Respiratory</td>
<td>34</td>
</tr>
<tr>
<td>Musculoskeletal &amp; Connective Tissue Disorders</td>
<td>28</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>26</td>
</tr>
<tr>
<td>Dermatology</td>
<td>25</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>22</td>
</tr>
<tr>
<td>Inflammation</td>
<td>21</td>
</tr>
<tr>
<td>Blood &amp; Coagulation Disorders</td>
<td>16</td>
</tr>
<tr>
<td>Gynecological, Urological</td>
<td>12</td>
</tr>
<tr>
<td>Hepatic</td>
<td>8</td>
</tr>
<tr>
<td>Dental &amp; Oral Products</td>
<td>4</td>
</tr>
<tr>
<td>Renal System</td>
<td>4</td>
</tr>
<tr>
<td>Wound Healing</td>
<td>3</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>2</td>
</tr>
<tr>
<td>Poison (Antidote)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Alliances with multiple therapeutic categories were counted more than once, in each of their respective categories.

SOURCE: Strategic Transactions
### Exhibit 4

**2015’s Top Money Grabbers: Cancer, Neurology and Infectious Disease**

*IPO And Venture Financing Transaction Volume By Company Therapeutic Area Of Focus*

<table>
<thead>
<tr>
<th>Therapeutic Area Of Focus</th>
<th>Transaction Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>112</td>
</tr>
<tr>
<td>Neurology, Nervous System</td>
<td>84</td>
</tr>
<tr>
<td>Infectious &amp; Viral Diseases</td>
<td>57</td>
</tr>
<tr>
<td>Metabolic Disorders</td>
<td>50</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>45</td>
</tr>
<tr>
<td>Musculoskeletal &amp; Connective Tissue Disorders</td>
<td>41</td>
</tr>
<tr>
<td>Immune Disorders</td>
<td>30</td>
</tr>
<tr>
<td>Respiratory, Pulmonary</td>
<td>28</td>
</tr>
<tr>
<td>Non-Specific</td>
<td>27</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>24</td>
</tr>
<tr>
<td>Inflammation</td>
<td>23</td>
</tr>
<tr>
<td>Dermatology</td>
<td>19</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>17</td>
</tr>
<tr>
<td>Blood &amp; Coagulation Disorders &amp; Products</td>
<td>16</td>
</tr>
<tr>
<td>Gynecological, Urological</td>
<td>11</td>
</tr>
<tr>
<td>Renal System</td>
<td>11</td>
</tr>
<tr>
<td>Hepatic</td>
<td>8</td>
</tr>
<tr>
<td>Wound Healing &amp; Tissue Repair</td>
<td>7</td>
</tr>
<tr>
<td>Dental &amp; Oral Products</td>
<td>2</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>2</td>
</tr>
</tbody>
</table>

*Financing deals were counted more than once if the company was involved in more than one therapeutic area.

SOURCE: Strategic Transactions
France’s drugs assessment agency wants simpler, stronger rules to evaluate the cost-effectiveness of new drugs. But changes to the country’s complex reimbursement system may be too slow to address immediate budget concerns, making pan-European bulk buying appear a more likely near-term solution.

In the light of the “colossal budgetary impact” of new medicines, France’s drug assessment and reimbursement agency, the Haute Autorité de Santé, is seeking to simplify, strengthen and clarify its evaluation methods, including those used to determine cost-effectiveness. The goals: a tighter link between cost-effectiveness and price, and more robust tools to measure the cost of innovation – without resorting to the kind of UK-style rationing that can lead to certain new therapies being denied reimbursement.

Indeed, although the latest version of France’s Social Security and Finance Bill, currently making its way through parliament, mandates shaving €1.6 billion ($1.7 billion) off the drugs bill, France still isn’t ready to adopt a cost per quality-adjusted life-year (QALY) threshold like the National Institute of Health and Care Excellence (NICE) in the UK. “That’s not realistic for France on the short term,” says Catherine Rumeau-Pichon, assistant director at HAS. She cites the need to take into account other factors such as unmet need and population size. Unsaid is the fact that a threshold remains politically unacceptable in this socialist country. And HAS, though nominally independent, has a government-appointed board and can only propose system changes; it can’t implement them without legislative backing.

What’s more, health technology assessment of any kind is relatively new in France: the country has only been carrying out cost-effectiveness analyses of individual drugs and devices since 2013. Before that, HAS looked almost exclusively at their clinical and medical benefit. The agency still doesn’t touch drug pricing – that is negotiated with drug companies by a separate body, the Comité Economique des Produits de Santé (CEPS). But, especially since the economic shock waves incurred by the arrival of Gilead Sciences Inc.’s revolutionary hepatitis C treatment Sovaldi (sofosbuvir) in 2014, HAS is talking more freely about cost, and about QALYs, that standard currency of health benefit. Indeed, the enormously wide variation in cost per QALYs calculated by HAS’ health economics division to date was cited by HAS as a key reason for its solicited changes. “The [costs per QALY] go from less than €10,000 to more than €200,000,” states an October 2015 release calling for the re-think.

If a threshold isn’t on the books, “more explicit advice” from HAS to the pricing authority, which negotiates with drug manufacturers, is, according to Rumeau-Pichon. She wants price negotiations aimed specifically at lowering a product’s incremental cost-effectiveness ratio.

In other words, HAS wants to sharpen the claws of its health economics arm (known as the Commission Evaluation Economique et de Santé Publique, CEESP). But it wants to do so without moving away from France’s negotiation-focused approach to drug pricing. Rumeau-Pichon refers to this as a “price-maker” approach: France’s system feeds clinical and cost analyses into subsequent price negotiations with pharma, whereas the UK, in contrast, takes a manufacturer’s requested price to calculate a cost per QALY, thus establishing what will or won’t be reimbursed. This “price-taker” approach can, and often does, lead to the UK’s refusal to reimburse certain products. (See “Calls For NICE Reforms Intensify After Early Enzalutamide Use Rejected” — “The Pink Sheet” DAILY, June 12, 2015.)

So how does HAS propose to improve “price-making,” without brandishing the big stick of reimbursement refusal (at least for innovative drugs; me-too’s or those deemed of insufficient medical benefit may already be denied reimbursement)? It’s not yet clear. But some answers may lie within an extensive report by economist Dominque Polton, a director at the French national insurance fund for salaried workers (CNAMTS). This document, commissioned by health minister Marisol Touraine early in 2015 and officially received in mid-December, critically assesses the criteria and methods currently used to value medicines, including the role of the CEESP. It has much to say about the system’s shortcomings, including a lack of coordination and understanding between the various decision-making bodies.

It duly proposes a more prominent role for cost-effectiveness analyses; clear, published reports using accessible language; and tighter integration of the CEESP with the clinical/medical evaluation commission. It also calls for more systematic measurement of the budgetary impact of new medicines.

The Polton report also proposes some more fundamental shifts to the structure of France’s underlying clinical evaluation process and reimbursement rules, however. And that’s no wonder, says a source from within HAS, because the whole lot is inextricably linked. “If you start to change the assessment criteria, you are forced to look at reimbursement rates,” explains the source. France’s current drug evaluation system involves two scales: one to determine absolute medical benefit (whether a drug or procedure will be reimbursed or not) and another additional medical benefit (which determines the rate of reimbursement: 15%, 30% or 65%). (See sidebar, “France’s Drug Reimbursement System.”) Neither addresses price. HAS has for years been seeking to merge these scales into a single, simpler index that strongly emphasizes comparative effectiveness (the index thérapeutique relatif, ITR). (See “Europe’s Future HTA Landscape: More Converged And Cost Conscious” — “The Pink Sheet,” January 14, 2013.)

Acknowledging this (and the fact that the ITR was considered overly rigid and formulaic), Polton proposes a relative therapeutic value score to replace the current additional medical benefit measure, with fewer, more clearly defined scoring categories. It also puts forward a single reimbursement rate (suggested at 60%) and eventually an end
to all reimbursement for products showing limited medical benefit. Such a set-up would be “more coherent, simpler and more in line with other countries’ practices,” Polton was reported as saying.

Health minister Touraine is expected to announce “within weeks” any measures that may be implemented as a result of this report. Moving to a single reimbursement rate doesn’t look likely, though, not least due to the public outcry that may result from de-reimbursing certain older products. “We’re not going to fundamentally change the system,” insists Rumeau-Pichon. She does foresee more performance-based pricing deals, though, and (as signaled in the report) more rigorous demands on drug firms, including sensitivity analyses using a wider range of pre-specified prices. This is still subject to discussion, however. And the report doesn’t deal directly with the public outcry that may result from de-reimbursing certain older products. “We’re not going to fundamentally change the system,” insists Rumeau-Pichon. She does foresee more performance-based pricing deals, though, and (as signaled in the report) more rigorous demands on drug firms, including sensitivity analyses using a wider range of pre-specified prices.

In the meantime, inter-national drug purchasing may prove the more effective and immediate, if rather blunt, method for lowering prices in some continental European nations. When Sovaldi hit the European markets, it was health minister Touraine who sought out inter-national collaboration to get the best price. That teamwork didn’t materialize for that drug – the proposal came too late to allow implementation, according to a source close to the discussions. “But that the suggestion was even made shows that things are moving,” the source continues.

Belgium and the Netherlands have already agreed to pilot joint-pricing talks for rare diseases drugs starting in 2016, boosting each small nation’s negotiating position. (See “European Notebook: Drug Pricing Collaborations; Biosimilar Switching; Scientific Advice” — “The Pink Sheet,” April 27, 2015.) “The wind is blowing in the direction” of more European-level price negotiation, concurs Rumeau-Pichon, though she’s quick to add that national-level reimbursement and pricing systems complicate matters. In an impactful October 2015 Forbes article examining drug pricing, Jack Scannell, an associate at the Innogen Institute and associate fellow at the Oxford, UK-based Centre for the Advancement of Sustainable Medical Innovation (CASMI), writes, similarly, that “European countries should buy as a block … and run competitive tenders to find the cheapest supplier for pan-European demand.” Scannell stamped his suggestion with a label of “hopeful implausibility.” But as more
targeted, innovative therapies reach the market, and absent the political will to say "no," bulk buying may prove the least complex solution. Indeed, "organizing buying power is the only way to come to any kind of negotiating position," declares Ad Schuurman, head of international affairs at the Netherlands’ health technology assessment and reimbursement agency. "Without it, it will be 'take it or leave it' for patients and health care systems," he says. A further tailwind for bulk buying: the Netherlands will hold the EU presidency during the first six months of 2016.

France negotiated one of Europe’s lowest prices for Sovaldi in 2014, without the help of any neighbors. But it did so by invoking a special additional tax on sales of companies selling HCV drugs, ushered into legislation at the last minute. Conjuring up a tax for each new expensive medicine is hardly a long-term solution to funding innovation.

Nor, deplores Les Entreprises du Médicament (LEEM), France’s drug industry association, is hitting drug costs for over half of the €3 billion health care budget cuts outlined in the new finance bill. The association, currently negotiating its next three-year umbrella contract with CEPS, is instead calling for fundamental structural reforms to the country’s health system, and for a broader focus on the downstream cost-savings that proper use of medication can allow. It’s a familiar refrain from the drug industry everywhere. But while drug prices remain in the hot seat, it’s falling on deaf ears.

LEEM wasn’t willing to comment on the suggested drug valuation and reimbursement changes prior to the official release of Polton’s report.

Melanie Senior

### FRANCE’S DRUG REIMBURSEMENT SYSTEM

#### STAGE ONE: TECHNICAL ASSESSMENT BY HAS’ EVALUATION COMMITTEE

This is a two-step process. The first involves determining a drug’s Medical Benefit (Service Médical Rendu, SMR), based on:

- efficacy/safety
- alternatives available
- disease severity
- treatment type (curative, preventative)
- public health impact

There are five levels of SMR, major, important, moderate, weak and insufficient. These determine the rate of reimbursement (100%, 65%, 30%, 15% or 0% [*insufficient* SMR]). The second step of the technical assessment is determining a drug’s added medical benefit relative to existing, comparable products (ASMR).

There are five ASMR levels, ranging from ‘major innovation’ to ‘no improvement’.

Drugs showing no improvement must be priced lower than comparators. The others may be priced higher, though only those in the top three categories (ASMR I-III) may be priced in line with other European countries.

Cost-effectiveness evaluations are carried out only on drugs showing an ASMR of I-III, likely to lead to annual costs of €20 million or more or which are likely to significantly impact care delivery.

#### STAGE TWO: PRICING NEGOTIATIONS WITH THE CEPS COMMITTEE

This is separate from the HAS evaluation committee, and includes representatives from mandatory and voluntary sickness funds, government ministries and industry.

These negotiations are opaque and it is unclear how HAS analyses (including cost-effectiveness) are taken into account and whether/how this links to price.

Re-assessment of reimbursement eligibility occurs every five years or when significant new information becomes available.

Melanie Senior

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A long period of waiting and many thousands of hours of debate are due to be brought to a close sometime in late spring 2016, when the EU’s new medtech legislation is adopted. Make that should be adopted, for the course of this twin set of regulations – the Medical Devices Regulation (MDR) and the In Vitro Diagnostics Regulation (IVDR) – has been less than smooth since the Commission launched the proposals way back in fall 2012.

EU stakeholders are now winding out of the “Trilogues,” a series of meetings in fall 2015 that were essentially for the Parliament and the Council to agree on two final, amended texts. The Parliament has concerned and angered industry in equal measure, insisting on additional regulatory “scrutiny” of high-risk devices (a job hitherto done exclusively by the Notified Bodies). It has also argued that all single-use devices should be seen as de facto reusable. Some of its ideas have been implausibly extreme.

A lot is at stake, as the new twin texts will be the cornerstones of the EU’s medtech legislation for the next 10 to 15 years. The need to balance patient safety with efficient market access for innovative products is felt keenly by medtech industry representatives in Europe, and none more so than by MedTech Europe (an alliance of Eucomed and the European Diagnostics Manufacturers Association [EDMA]) chief executive Serge Bernasconi. For the past three or more years he has been hopeful that a sense of balance will prevail, but when IN VIVO spoke to him at the 2015 European MedTech Forum meeting in Brussels, Belgium, last month, his mood was one of frustration.

“The Trilogues are not moving as quickly as we would like, or in the way we want,” said Bernasconi. Medtech companies need to prepare and anticipate the changes ahead, but they have little idea of what to expect, or when. “The lack of clarity created is not viewed favorably by companies and VCs that want to invest in Europe, and they have a tendency to start looking at other regions,” he said.

Bernasconi continued: “They want predictability and we can’t give them that. It’s time we moved to a conclusion, but the thing we’ve highlighted for many years is that these dossiers are complex. Industry supports the need for change, both on the IVD and the medtech side. And if we want a system in Europe that is respected and trusted, and not open to criticism from concerned patients who are anxious about the quality of device assessments, then it is time for us to develop something new.”

Industry is willing to pay the cost, to accept the increased complexity, and to accept that it might take more time to develop an appropriate system, said Bernasconi, but he stressed: “It has to have value.”

As Bernasconi spoke, on December 3, the scheduled program of five Trilogues, each taking a large theme or a number of smaller ones, was drawing to a close. However, it was looking increasingly unlikely that the Luxembourg Council presidency (July–December 2015) would complete the task of finalizing the texts – although not for the lack of ambition. So the baton was passed on January 1, 2016, to the Netherlands to continue the task under its six-month rotating EU presidency.

There was criticism that the Trilogues were conducted behind closed doors, and keeping updated on the course of the debates was fairly impossible. The series may have kept to schedule, but Bernasconi bemoaned the fact that there had been an absence of agreement on any of the key issues, like the clinical evidence requirements, additional scrutiny process, and regulation of the reuse of single-use devices. “They seemed to keep putting the same themes back on the table,” he said.

The whole issue of what clinical evidence will be required remains under discussion. The processes in place for the pharma industry are often invoked by those seeking to back up the notion that all health care products (medtech and pharma) should have to supply similarly high levels of evidence. Devices need good and solid preclinical information, Bernasconi agreed, but people often forget that devices have users as well as end patients. “That’s a variable that you can control only up to a point,” he said.

For instance, in a preclinical set-up, companies can engage the best clinicians and top engineers to secure the necessary trial results. But in a live market situation, that cannot happen as a matter of course. “More preclinical data can be provided by companies, but that does not reproduce what goes on out in the field,” Bernasconi pointed out. “We have always said that the right balance needs to be struck between preclinical evidence requirements and well-organized, followed-up post-market surveillance.”

It’s a dilemma for companies that are not sure of what level of evidence to supply. “But I see too much focus right now on preclinical evidence, and people are wrong on that,” Bernasconi asserted. “They are expecting to get a 100% total and full picture from this, but they won’t get it.”

Industry is committed to training physicians, said the Eucomed chief executive, but there is only so much training that it can do.

The pharma sector has randomized controlled trials, and “we’re not actually saying no to them, but we are asking seriously, ‘Just how do you implement them for devices?’ In some cases, it’s just impossible,” he said.

Evaluating the clinical evidence of IVDs is a different matter and poses another problem. “How do you judge an IVD?” asked Bernasconi. “It’s not a drug or a device. It rarely comes into contact with the patient – some self-tests apart – so the safety aspects must also be considered differently.” Moreover, doing tests at different times of the day might produce different results.

The EU medtech industry is not opposed to health technology assessment (HTA), but there is a lack of awareness as to how to evaluate a device, said Bernasconi. The drug evaluation system cannot simply be dropped on top of devices. And the value of a device needs to be considered over, say, five years, to get the full impact of that value. At present, too many of them are expected to show value more or less immediately, that is, within a year.

This shows a lack of vision on the part of the providers and payers. Industry can take the initiative by setting up a dialogue with national health system procurement departments. Reimbursement and procurement
are national issues in Europe, although DG Sanco/DG Santé (the directorate general dealing with food safety and other regulatory issues) is getting more involved, Bernasconi said, adding that the EU could at least play an alignment and coordination role in this area.

The “scrutiny” debate has proved even more controversial. Bernasconi recognizes that there is a political will in certain EU circles to introduce extra layers of regulatory scrutiny for high-risk devices, but thinks these efforts are pointless. “Sadly, it will not bring any increased safety for patients,” he said.

Better were the Commission’s actions in fall 2013 when it issued two texts, one a regulation and the other a recommendation, that were aimed at elevating the standards for Notified Bodies. Bernasconi says it is crucial that the Notified Bodies do a good job, and in the future they will probably take on the added extra element of clinical evaluations. Most of them (currently numbering some 62 and expected to fall to 40 or even fewer over time) will have to acquire that additional expertise.

“Strong controls on NBs would obviate the need for the scrutiny process,” said Bernasconi. But at the same time industry is expecting some sort of show of strength from the Parliament, so MEPs can claim that they have “put safety mechanisms” in place.

This is not good for the EU industry nor indeed any element of the health care chain. The EU time-to-market for devices might lengthen. And the reason for implementing these new checks and controls is built on a false premise. “A check shows there are not more device problems in the EU than in the US, and that products get to the EU market on average three years quicker than in the US,” said Bernasconi.

Indeed, the EU has not had any significant problems, aside from the infamous PIP breast implant case, but that was fraud and deception on the part of the manufacturer, which effectively side-stepped its regulatory duties. Moreover, the appeal of the EU system, regardless of whether it needs to be overhauled, is not diminished. “A lot of countries around the world are interested in implementing the EU regulatory model” Bernasconi stated.

The US FDA, for its part, has recognized that it went a bit too far in its regulatory demands, and of late there have been strong efforts by the US agency to simplify the system and speed up device approvals. This has to be good for all US stakeholders. “In Europe, on the other hand, we seem intent on going in the opposite direction, at the risk of making the EU less attractive than it once was,” said Bernasconi.

The risks of going too far are now closer to reality. “We must be very careful that we don’t turn the EU system into some sort of dinosaur that nobody can work with anymore,” Bernasconi said. The danger is there, and it could have a very negative impact on the innovation cycle in Europe. There would be the real prospect of cardio, neuro and ortho innovators leaving the EU to develop their technologies in areas that have lower regulatory barriers. China, for instance, is doing more R&D. “The country is becoming truly competitive as a research pole,” said Bernasconi, adding a warning: “Do not underestimate them.”

There are very few mature, job-creating device companies in Europe, he observed. The question is “Are we interested in creating — keeping and sustaining — a European medical device industry? If we are, how do we help start-ups and SMEs go through the first five to 10 years of their lives?”

An overly challenging pre- and post-market system with an expensive and lengthy pathway is not the answer, and start-ups would run a high risk of failing or would have to go in with larger companies at an earlier stage. The wider industry gets a lot of innovation from start-ups. “That is the basic model of this industry, and we need to be sure that these additional regulatory complexities do not dry up that flow. There is a real risk of that,” Bernasconi said.

But in this new environment, industry has to help itself, too. It must be able to demonstrate the economic contribution and value that its products represent. The sector has moved on from the times when it was purely technology driven. “Show the added value,” Bernasconi advises manufacturers.

The industry has in fact started to do this over the past five years or so, but it needs be systematic. “It’s expensive and complex for industry, but it needs be done,” he stressed.

For the MedTech Europe chief executive, the major preoccupation is the lack of forward motion on the new EU regulatory systems for devices and diagnostics. “It keeps everything hanging in the air, and it’s not good for the development of the industry,” said Bernasconi, adding: “Let’s get it going and get into the nitty-gritty of these issues.”

Ashley Yeo

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**2015 DEALS OF THE YEAR**

**TOP ALLIANCE:**
**CELGENE IN I/O**

*35% OF THE VOTERS CHOSE* CELGENE, which struck deals with Medimmune, Nurix and Juno Therapeutics in 2015 to establish itself as the leader in the red hot immuno-oncology field. Sanofi and AstraZeneca’s asset swap was a distant second with 17% of the vote.

**TOP M&A:**
**PFIZER/ALLERGAN**

*44% OF THE VOTERS CHOSE* Pﬁzer and Allergan’s $160 billion merger, the biggest deal in health care history. Runner-up Teva’s $40 billion acquisition of Allergan’s generic business came in second with 29% of the vote.

**TOP FINANCING:**
**IRON HORSE THERAPEUTICS’**

*52% OF THE VOTERS CHOSE* GRox’s $10 million Series A round. It was far from the biggest financing of the year, but this seventh launch from GlaxoSmithKline and Avalon Venture’s build-to-buy machine was the runaway winner in this category.

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*We nominated 18 deals in three categories, and readers cast their votes.*
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The technology-driven medical device industry: that’s so 2014. The 2016 medtech executive has other things on his/her mind, and they all come under the general job title of “value-based health care delivery chain partner.” Titles are not as simple as they once were, and while no one yet wears that precise title on his/her lapel badge (come to that, lapels are not what they once were), medtech companies in the 2010s know they are playing in a totally different arena and are part of an industry in transformation.

This has happened due to the convergence of several factors related to provider/payer cost savings, rising demand for care, a relentless push for quality in patient outcomes, dwindling interest from venture capitalists, a tougher reimbursement environment and the waning attraction of working in primary and secondary care as it is currently structured. And chiefly, the slowing down of medtech market growth: Europe is expected to see medtech market CAGR of a lowly 2% to 3% in the period 2015–2020, and the US, 3% to 4%. It’s a sobering outlook. Those values are projected in a Boston consulting Group report on transforming business models. It is yet to be released (scheduled, fall 2016), but IN VIVO was granted early access to its findings, which showed that companies are adapting to the new pressures on them and their markets. (See “Medtechs Told: Change Commercial Models Or Be Left Behind” — IN VIVO, December 2015.) But although the changes are starting to happen, progress is slow. In 2016, companies will have to be a lot more serious about: pricing and reimbursement pressures, meeting the demand from decision-makers for better-value products, and the fact that these decision-makers per se are increasingly less the clinician, and increasingly more the economic decision-maker.

Chiefl y, they must be able to demonstrate the economic contribution and value that their products represent. Visionaries and health economics and outcomes research (HEOR) specialists may have foreseen such developments many years ago, but the sector has now, definitively, moved on from the time when it was purely technology driven. MedTech Europe chief executive Serge Bernasconi, a veteran of senior US and EU corporate roles at Johnson & Johnson, Medtronic and Schering-Plough, believes modern-era manufacturers will ignore the current trends at their peril.

Speaking to IN VIVO during the European association’s annual meeting in Brussels, last
December, he said that innovators must “show the added value. It’s an expensive and complex task for industry, but it needs to be done, and in a systematic way.”

You have been warned.

The evolving US payer and provider system already expects manufacturers with new medtech products coming onto the market to pre-think the system value of their innovations. The US-centric – some say, excessive – 30-day hospital readmission penalty pressure is also prompting companies to think differently about how to get their higher-value solutions into the system.

In 2015, St. Jude Medical Inc. offered a good example of adapting the approach to evolving needs, with data from its heart failure treatment trial (CHAMPION) showing that hemodynamic monitoring with the St. Jude remote CardioMEMs system can reduce readmissions by up to 50%. (See “St. Jude’s CardioMEMS Showing Results In HF” — IN VIVO, December 2015.) HF is on course to be a $60 billion burden in the US by 2030, and is already costing $31 billion annually, according to the American Heart Association, almost half of which is ascribed to the costs for the more than one million associated hospitalizations.

Elsewhere, US Integrated Delivery Networks (IDNs) – inpatient and outpatient networks that offer a continuum of care – are changing the complexion of US health care business practice, and manufacturers that want to keep their stake in the system need to undergo a change management process and to ensure they know how to work with IDNs.

Senior principles at IMS, speaking to IN VIVO in mid-2015, stressed that industry needs to be mindful that, five to 10 years out, as IDNs and payers consolidate, this will become an all-or-nothing game. So companies must start getting it right as of now.

It is a question of delivering quality in an outcomes-based environment, and industry can lead in this “or be dragged.” (See “Pharmas Urged To Take Committed Steps Along The IDN Pathway” — IN VIVO, December 2015.)

Leadership is an increasingly important quality for medtechs to aspire to, and one real example of what it means to lead is when manufacturers embrace lower-cost models that contribute to broad improvements in outcomes and population management.

And even commodity companies will have to take on some element of risk with providers. Delegates at AdvaMed’s annual meeting in fall 2015 heard examples of how medtech CEOs are beginning to engage with providers and payers in order to do business in new ways. Similarly, companies are trying new methods of bringing value into the equation, and this is transforming the way they operate.

This was the take of EY executives, speaking to IN VIVO in the fall after the release of their company’s latest Pulse of the Industry report. (See “No End In Sight For M&A As Medtechs Adapt To The ‘New Normal’” — IN VIVO, November 2015.) But medtech executives don’t find it easy to break out of the unit-price-economics mind-set. In many cases, medtech firms are still trying to define their new role in the transforming industry. Because they are struggling with this, patience will be needed on their part.

The whole ecosystem approach applies not just to medtech, however. It is thought that providers do not yet really have an appreciation of the arrangements they need to set up, or how to value them. But many are moving to untied yet compelling new models of care.

The budget-pressured UK, with its Beveridge model of tax-funded universal care (free at the point of delivery), is one of these. The UK is in the second tier of global medtech markets by size, but the health care system’s transparency and its efforts to adopt sustainable, affordable and efficient delivery make it worth studying in an international context.

NHS England in 2015 gradually began introducing five new care models (NCMs; integrated primary and acute care systems, enhanced health in care homes, multispecialty community care urgent and emergency care, and acute care collaborations) that essentially represent a complete redesign of the whole health and care systems in a bid to break down the barriers between the component parts of care delivery. Providers are signing up to “vanguard” sites for the new models to effect the change. Eventually, it is foreseen that these NCMs will lead to fewer trips to the hospital, shorter stay lengths, local access to services and care closer to home.

The concept is at its earliest stages still, and it is happening moreover alongside other initiatives to make medtech savings (the Lord Carter Review), faster availability of innovative medtech and pharma products (the AAR – Accelerated Access Review), regionally devolved health care budgets and, eventually, a single budget for health and social care. The effects on medtech providers will be direct, immediate and lasting.

Longer term, it is foreseen that more medtech companies will move into the provider space, following the examples already being seen for some long-term conditions like CHF and diabetes. Progressive models are also to be observed at companies such as Fresenius Medical Care AG, which has been buying up urgent care and other provider-like services; Stryker Corp., with its penetration of the reprocessing space via its Ascent Healthcare Solutions Inc. purchase (a way of addressing the costs by prioritizing device reprocessing); and Medtronic PLC, which ramped up its position in heart failure with the acquisition of disease management and patient-monitoring firm Cardiocom some two years ago, putting it firmly in the remote provider space.

CARDIO DOMINATES TOP M&A IN 2015

If partnering with providers and payers is a relatively recent phenomenon, the traditional form of collaboration for medtechs – industry M&A and dealmaking – is still taking place at very high levels in 2015, (see Exhibit 1.) and according to the consensus,
levels will be maintained into 2016.

Two of the major M&A episodes of 2015 had their roots in 2014. One, Becton Dickin - son & Co.'s $12.6 billion cash and stock acquisition of 100% of CareFusion Corp. was announced in October 2014, but was completed on March 17, 2015. The combination produced a global leader in medication management and patient safety solutions that made combined sales of $10.3 billion in BD's fiscal year ended September 30, 2015. This included CareFusion sales as of April 1, 2015.

BD chairman, CEO and president Vincent Forlenza said in a major interview with IN VIVO that the merger was not merely a narrow tactical sales volume transaction, but a strategic “solutions play” that meets the evolving needs of stakeholders. For BD, the deal is also an opportunity to employ a whole pharmacy-to-patient approach in the medication management business, and a basis from which to step up its focus on China and target the emerging markets and new geographies with its broader range of medication management and infection control solutions. (See “Becton Dickinson Adds A Bigger Jewel To Its String Of Pearls” — IN VIVO, September 2015.)

The time of old business models has passed, as BD observed that both the industry and the post-Affordable Care Act US government have changed. BD’s reasoning was that it could play a much more enhanced role by moving from being a company with a narrow product focus to one with a solutions-oriented mentality. The deal also gave the combined concern more product breadth, which is a useful tool in its work with IDNs and providers.

The world’s largest pure-play medtech company, Medtronic (with which BD set up a diabetes partnership in 2015) kept up a healthy pace of M&A in 2015. (See Exhibit 2.) In 2014, its 2015 Covidien PLC mega-deal – which was just as much about getting product diversification (i.e., more 510ks vs. PMAs) as tax inversion and other aspects – elevated it to number two (all medtech branches) in the global ranking, behind Johnson & Johnson. But for how long will J&J lead the pack, observers wonder?

J&J’s 2015 sale of Cordis Corp. was flagged in IN VIVO’s 2014 medtech review. The 2016 major names to watch must include the orthopedic firms Stryker and Smith & Nephew PLC. It is increasingly difficult to list 20 truly major ortho companies that are publicly quoted and/or disclose sales values, and that task may become even harder after 2016 now that we have learned that the US firm is circling the UK company once more. In 2014, Stryker’s $4.9 billion ortho sales were half those of market leader DePuy Synthes, and in 2015 it has fallen behind Zimmer Biomet Holdings Inc. The $3.3 billion (in 2014) S&N group is the largest “independent” ortho remaining, and it represents the quickest route for Stryker to continue to accelerate the top line and challenge market leadership during this sustained period of low-level organic growth.

There were 17 $1 billion+ deals (excluding the deals announced in 2014 but completed in 2015 – BD/CareFusion and the $3.3 billion merger of top 20 ortho players Wright Medical Technology Inc., of the US, with Tornier NV, of the Netherlands. A single theme in major M&A was hard to identify in 2015, but if one field did stand out, it was cardiovascular (although it was run close by activity in the patient monitoring/IVDs field). The cardio deals included:

- Johnson & Johnson’s $1.994 billion deal to sell its interventional cardiology business, Cordis, to Cardinal Health Inc., whose strategy is to offer high-value, commoditized products in a cost-efficient way;
- St. Jude Medical’s acquisition of the outstanding shares in ventricular-assist device maker Thoratec Corp., effective as of fourth-quarter 2015, for $3.3 billion in cash. St. Jude has historically tended to eschew large acquisitions (the 2005 purchase of Advanced Neuromodulation Systems Inc. aside). The rationale of bringing the two heart failure therapy leaders together was to secure a unique offering for physicians and patients across the heart failure continuum;
- Greatbatch Inc.’s purchase of privately owned Lake Region Medical Holdings Inc. (formerly Accellent Inc.), in a deal valued at about $1.73 billion to create a 9,000-employee outsourcing company that services the cardiac, vascular, orthopedics and advanced surgical markets in the US, Latin America, Europe and the Asia-Pacific regions. The rationale here is that drug and device makers are increasingli looking to outsource manufacturing in the rapidly consolidating health care industry; and
- Italian cardiovascular company Sorin Group SPA and US neuromodulation specialist Cyberonics merging, with effect from October 19, to form a new entity, LivaNova PLC, a group with enhanced critical mass and thus better chances of winning tender-driven hospital contracts. Combined, these two mid-caps have pro-forma sales of around $1.3 billion.

Many wonder when M&A activity will slow down, as it must at some point. But that may not be for a while yet. The mega-deals trend continued into 2015, with Pfizer Inc. offering $17 billion for Hospira Inc.’s injectable drugs, infusion technologies and biosimilars business, and Danaher Corp. taking over Pall Corp. in a $13.8 billion deal. These were the leading mega-deals of 2015. The full list is below.

The consensus is that there is more major
## Exhibit 1

### Medtech Mega-Deals In 2015

<table>
<thead>
<tr>
<th>BUYER</th>
<th>TARGET</th>
<th>BUSINESS ACQUIRED</th>
<th>DEAL VALUE</th>
<th>ANNOUNCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer (US)</td>
<td>Hospira (US)</td>
<td>Infusion pumps as part of biosimilars, pharma package</td>
<td>$17bn</td>
<td>Feb. 5 (completed Sept. 3)</td>
</tr>
<tr>
<td>Danaher (US)</td>
<td>Pall (US)</td>
<td>Filtration tech</td>
<td>$13.8bn</td>
<td>May 13</td>
</tr>
<tr>
<td>Dentsply (US)</td>
<td>Sirona Dental Systems (US)</td>
<td>Dental systems</td>
<td>$13.3bn stock swap</td>
<td>Sept. 15</td>
</tr>
<tr>
<td>St. Jude Medical (US)</td>
<td>Thoratec (US)</td>
<td>Cardiology heart assist devices</td>
<td>$3.4bn</td>
<td>July 22</td>
</tr>
<tr>
<td>Excelsior Union (China)</td>
<td>Mindray Medical (China)</td>
<td>IVD/patient monitoring/imaging</td>
<td>$3.3bn</td>
<td>Nov. 4</td>
</tr>
<tr>
<td>Mallinckrodt (US)</td>
<td>Ikaria (US)</td>
<td>Neonatal critical care</td>
<td>$2.3bn</td>
<td>March 5</td>
</tr>
<tr>
<td>Hill-Rom (US)</td>
<td>Welch Allyn (US)</td>
<td>Diagnostics/patient monitoring</td>
<td>$2.05bn</td>
<td>June 17 (completed Sept. 8)</td>
</tr>
<tr>
<td>Cardinal Health (US)</td>
<td>Cordis (J&amp;J)</td>
<td>Cardiology and endovascular</td>
<td>$1.944bn</td>
<td>March 2</td>
</tr>
<tr>
<td>Greatbatch (US)</td>
<td>Lake Region Medical (US)</td>
<td>Cardio/vascular and other segment outsourcing</td>
<td>$1.73bn ($478m cash, $1bn debt &amp; 5.1m shares and options issued)</td>
<td>Aug. 28</td>
</tr>
<tr>
<td>Boston Scientific (US)</td>
<td>American Medical Systems’ Endo Health Solutions urology portfolio (US)</td>
<td>Urology</td>
<td>$1.6bn up front and maximum $50m milestone</td>
<td>March 2 (completed Aug. 4)</td>
</tr>
<tr>
<td>OPKO Health (US)</td>
<td>Bio-reference Laboratories (US)</td>
<td>Diagnostic labs</td>
<td>$1.47bn</td>
<td>June 4</td>
</tr>
<tr>
<td>Mallinckrodt (US)</td>
<td>Therakos (US)</td>
<td>Immunotherapy via extracorporeal photopheresis</td>
<td>$1.3bn</td>
<td>Aug. 10</td>
</tr>
<tr>
<td>Cinven (UK)</td>
<td>Labco (France)</td>
<td>Diagnostic labs</td>
<td>€1.2bn/$1.3bn</td>
<td>May 29</td>
</tr>
<tr>
<td>Roche (Switzerland)</td>
<td>Foundation Medicine (US), majority stake</td>
<td>Molecular diagnostics</td>
<td>Up to $1.18bn</td>
<td>Jan. 12</td>
</tr>
<tr>
<td>Panasonic Healthcare (Japan)</td>
<td>Bayer’s diabetes care business</td>
<td>Diabetes management</td>
<td>€1.02bn/$1.15bn</td>
<td>June 10</td>
</tr>
<tr>
<td>IBM (US)</td>
<td>Merge Healthcare (US)</td>
<td>Medical image handling and processing</td>
<td>$1bn</td>
<td>Aug. 6 (completed October 13)</td>
</tr>
<tr>
<td>3M (US)</td>
<td>Polypore International’s separations media (US)</td>
<td>Membranes for medical devices, life sciences</td>
<td>$1bn</td>
<td>Feb. 23</td>
</tr>
</tbody>
</table>

SOURCE: IN VIVO Research
Top Of The Top Lines – Medtronic’s M&A Path To Global Leadership

<table>
<thead>
<tr>
<th>TARGET</th>
<th>BUSINESS ACQUIRED</th>
<th>DEAL VALUE</th>
<th>ANNOUNCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twelve Inc. (US)</td>
<td>Cardiology – transcatheter mitral valve replacement</td>
<td>$408m plus $50m milestones</td>
<td>Aug. 24, 2015</td>
</tr>
<tr>
<td>Medina Medical Inc. (US)</td>
<td>Neurology – embolization device</td>
<td>$150m plus milestones</td>
<td>Aug. 31, 2015</td>
</tr>
<tr>
<td>Aptus Endosystems Inc. (US)</td>
<td>Cardiac surgery</td>
<td>$110m</td>
<td>June 19, 2015</td>
</tr>
<tr>
<td>CardiolInsight Technologies Inc. (US)</td>
<td>Cardiac rhythm management</td>
<td>$93m</td>
<td>June 19, 2015</td>
</tr>
<tr>
<td>Aircraft Medical Ltd. (UK)</td>
<td>Patient monitoring – handheld video laryngoscope</td>
<td>Undisclosed</td>
<td>Nov. 18, 2015</td>
</tr>
<tr>
<td>Diabeter (the Netherlands)</td>
<td>Diabetes care provider</td>
<td>Undisclosed</td>
<td>April 2, 2015</td>
</tr>
<tr>
<td>Sophono Inc. (US)</td>
<td>Hearing aids</td>
<td>Undisclosed</td>
<td>March 26, 2015</td>
</tr>
<tr>
<td>Advanced Uro-Solutions (US)</td>
<td>Neuromodulation</td>
<td>Undisclosed</td>
<td>Feb. 23, 2015</td>
</tr>
</tbody>
</table>

SOURCE: IN VIVO Research

M&A to come. Relatively cheap access to capital in the credit markets, the ability of M&A transactions to take costs out of the system, and the resulting enhanced cash flow and cash generation means mega- and sub-$1 billion deals are still looking attractive. EY’s view is that the M&A lever is likely to be pulled a few more times, and that the industry will continue to see large-scale M&A, all the while there are opportunities for more Biomet-Zimmers and BD-CareFusions.

MEDTRONIC MAKES ITS INTENTIONS CLEAR
Whereas long-time global medtech market leader Johnson & Johnson selectively adjusts its medtech assets in a disciplined portfolio management approach that is designed to streamline the business, reduce costs and focus on the most promising opportunities that drive growth, the contender for global market leadership, Medtronic, is selectively growing its top line in a more aggressive way.

The Covidien adjustments from the 2014 deal are still being worked on, and only a single quarter of sales were consolidated in Medtronic’s latest annual figures. Meanwhile, the group has not rested on its laurels. In fact, in 2015 it disclosed no fewer than eight M&A transactions, of varying size and in different market segments. It was the most prolific of the major players.

All the while J&J makes the headlines for asset disposals – the 2015 sale of Cordis (flagged in IN VIVO’s 2014 medtech review) followed its 2014 sale of the major IVDs company Ortho-Clinical Diagnostics Inc. – if current trends continue, it cannot be long before Medtronic (sales in FY 2015, $20.3 billion) overtakes J&J’s medtech top line (FY 2014, $27.5 billion)

In fact, the sales gap has reduced to $7.2 billion in Medtronic’s FY 2015, from $11.5 billion in the previous year, and Medtronic gained over $3 billion worth of sales, whereas J&J lost just under $3 billion in sales. Medtronic has already overtaken GE Healthcare, and sales in its FY 2016 could well put it at the head of of the global medtech sales ranking.

OTHER FACTORS IN THE MEDTECH MIX
If Medtronic’s approach is typical of the wider medtech sector’s mood (if not necessarily its ability to follow suit), the industry has reached an inflexion point, where medtechs have realized that there is virtue in expanding product portfolios, engaging in M&A and investing in R&D to drive growth.

Medtech has in fact increased its R&D spend for five straight years, and in 2014–2015 it returned less cash to shareholders via dividends and share buybacks than in previous years. This is taken as a sign that greater priority is being placed on investing in innovation, widely seen as crucial for medtech’s growth prospects. On the other hand, breakthrough innovations arise only rarely, and growth via incremental innovation in the value- and evidence-based environment of 2015–2016 is more difficult to achieve than it was a mere decade ago.

In 2014, the global medtech market nudged up by just 2% to $342 billion, says EY’s 2015 Pulse report. Two percent to 5% growth is expected in both of the years 2015 and 2016. This is far away from the golden era of double-digit sales, but those with an eye on the trend and a finger on the industry’s pulse are adjusting their business models and market approach strategies to ensure they are playing a role in steering the market of the future.

Alongside a healthy M&A market – with more mega-deals in 2015 than in 2014 – there have been high numbers of IPOs (27 completed, with eight still pending at December 23, against 36 in 2014). But concern is shared around the globe at the low levels of – and trend in – VC financing (i.e., becoming later-stage) of medtech start-ups. Medtech is not a priority investment arena right now, it seems, attracting only 5.9% of all US venture dollars in 2014.

AdvaMed chairman Vincent Forlenza (also BD’s chairman, CEO and president) has observed that first-time funding for medtech start-ups dropped by almost 75% over the period 2007–2013, and industry is concerned that there is not enough seed corn to fund the small medtech companies that are often the source of innovation and/or M&A.

MedTech Europe’s Bernasconi is of the
same mind. Start-ups provide the wider industry with a lot of innovation, and stakeholders have a duty to do what they can to ensure that the new – and to-come – regulatory complexities do not dry up the flow of innovation.

**Pitfalls and Opportunities in 2016**

How companies adjust to the new demands, threats and opportunities in a constantly evolving sector is what separates the successful and pragmatic from the rest. In 2016, there will be both threats and opportunities arising from changing regulatory codes in the US and other market access hurdles. (See sidebar, “Things Are Looking Up On The US regulatory/Policy Front.”) The top talking points are listed below.

**New Medtech Regulations – IVDR and MDR – in Europe**

**Threat:** Regulatory uncertainty is one of the key concerns for the industry in 2016 – in the EU and the US. The EU is finally bringing many years of work to close in first-half 2016, when it settles on two new regulations (the Medical Devices Regulation – MDR, and the In Vitro Diagnostics Regulation – IVDR) that will govern safety issues regarding the placing on the market of medical devices and IVDs. (See “IVD Companies Brace For EU Regulatory Changes” — IN VIVO, October 2015.) But as they stand, they are restrictive (including extra scrutiny of high-risk files), potentially inappropriately tough (senseless and inappropriate clinical evidence requirements), and dangerously out of kilter with current patient safety standards (the European Parliament’s drive to liberalize the reprocessing of single-use devices). Moreover, the uncertainty surrounding the new legislation – which is seriously behind schedule – is making VCs ever more hesitant about investing in start-up EU technologies, prompting fears that the local R&D base will shrink and the flow of innovation may slow as a result. The cost of compliance with the new regulations will not be without fallout in the company ranks: for IVDs, the cost has been put at an additional €2 billion over the next five years. For these reasons, MedTech Europe sees this theme as the biggest item on the EU’s medtech agenda in 2016. As a risk factor, none surpasses it at present.

**Opportunity:** The three EU directives that are being replaced by the two regulations are 17, 22 and 25 years old, respectively, and were in need of updating to keep pace with the technology evolution. Many see the chief benefit of the EU regulatory overhaul as better and equal standards of file assessment across Europe by the Notified Bodies, which are seen widely as the weak link in EU regulation, even though the top tier operate under the highest standards globally, participate in voluntary assessments and sign up to codes of conduct. Many EU Notified Bodies have disappeared already and more are sure to follow as the 2014 headline figure of 82 NBs wanes to some 60 at present, maybe settles at or below 40 when the process has ended and the MDR and IVDR are both implemented, by 2019 and 2021 (not yet confirmed), respectively.

**New Models of Care and Evidence Generation**

**Threat:** Health care systems have long talked up the need to put quality and outcomes on an equal footing with affordability, but now as manufacturers are finding out, this is no longer merely non-binding guidance. The UK, for instance, is grappling with delivery model change (see above), and manufacturers are impatient to hear how they are expected to change their own approaches. Manufacturers cannot let the case for product adoption rest merely with the technological aspects, but need to ensure that evidence-based arguments succeed by keeping in mind national policies, priorities, targets, disease patterns, staffing shortages and capacity constraints. In the US, IDN networks are having a major influence on the prescribing patterns of physicians. Not being in the IDNs system is simply not an option for manufacturers, bearing in mind the Centers for Medicare and Medicaid Services’ drive, via multiple payment models, to move from fee-for-service to fee-for-quality.

**Opportunity:** The new game for medtechs is all about delivering quality in an outcomes-based environment, and it need not be viewed negatively. In the case of the US IDNs, manufacturers cannot ignore their influence and importance, and are advised to start slowly with their engagement and understand what stakeholders want to achieve. The reality is that companies must tailor the value proposition to help the IDNs achieve their goals – requiring a very thoughtful, measured and committed investment. Reimbursement strategies — in the US and elsewhere — will no longer succeed without strong, evidence-based messages about why the product should be adopted. Also essential are messages that show that the product is cost-effective (i.e., offers value for money) and affordable.

**New Technology Themes That Affect Medtech Business Models**

**Threat:** With high-tech players like Microsoft, Apple and Google getting more and more news coverage and becoming more serious about medical devices, established medtechs look at their disruptive threat with a wary eye. Elsewhere, uncertainty over what level of app needs what level of regulation is a murky cloud over the sector as it continues to grow exponentially.

**Opportunity:** But in reality, medtech has always evolved over the decades by adjusting its business model to key emerging technologies (KETs), and consumer IT connectivity – digitalization, apps, medical/c clinical wearables, sensors – is just the most recent of them. The medical devices sector has always worked with IT, but all that happens in IT has a huge influence on the industry. MedTech Europe’s Bernasconi describes the opportunity before the industry as “really exciting,” and manufacturers need to look at technologies being developed by the high techs and assess how they should collaborate with these firms, bring the technologies into medtech and move the industry forward. Two related major opportunities in this field for 2016 are the leveraging of connectivity to help bring patients out of the expensive hospital setting and bring them into the home setting, and how industry can use the opportunities that are arising from the “big data” revolution.

**New Technologies Coming into Use**

**Opportunity:** Medtech’s success with payers and providers may no longer be technology driven, but technology improvements will always continue to extend and improve the quality of life. For an indication of the industry’s continued breadth of inventiveness, look no further than Cleveland Clinic’s annual list of Top Ten Techs. In an industry rich in innovation, its medtech solutions lists are always a good indication of the state of
G
oing in to 2016, it’s hard not to characterize the US regulatory and policy environment as positive for the medical device industry. There is a consensus that the FDA premarket review process in 2015 has become, on average, more efficient and more transparent that it was five to 10 years ago. And policymakers, if anything, are focused on furthering that trend.

Device provisions passed by the US House of Representatives in the 21st Century Cures in July, including a “breakthrough” device pathway, are almost wholly focused on getting products or product modifications to market faster. (See “Cures’ Bill Passes, As More Budget, Safety Debates Wait In The Wings” — “The Gray Sheet,” July 10, 2015.) The US Senate will be the place to watch in 2016 to see if some or all of the reforms will carry through to law.

It is by no means a sure thing that a Cures-like bill will be enacted, especially due to the unpredictable nature of Congress during a presidential election year, but events so far make clear that the device industry has the ear of important power-players in Washington, DC. That is even more evident from the industry’s recent partial success in its long struggle against the medical device excise tax, which was enacted under the comprehensive health care reform bill in 2010. In year-end legislation, a two-year suspension of the tax was enacted. (See “Two-Year Ban On Device Tax Approved In Tax-Extenders Bill” — “The Gray Sheet,” December 16, 2015.) Although this falls short of the sector’s ultimate goal of full repeal, it’s an achievement for President Obama to have signed any measure that cuts into the funding for his signature health care policy and it might be the first step towards repeal.

For industry lobbyists, one of the main targets in 2016 will be improving the reimbursement environment for innovative devices. Many companies argue that while the FDA process is smoother, big-ticket devices are trying to enter the market without a clear path to payment. FDA and the Centers for Medicare & Medicaid Services have in recent years become more and more collaborative in efforts, officials say, to help streamline the path from approval to reimbursement. Efforts so far have focused on a very limited subset of devices, and companies are discussions with the agencies, and with Congress, about establishing a more automatic, but temporary, path to reimbursement for certain types of products that would allow time for data to be collected to support long-term cost-effectiveness arguments. Government officials say they are willing to be creative, but point to a lack of resources as one impediment. (See “Breakthrough Reimbursement Proposals Percolate From FDA, Industry” — “The Gray Sheet,” October 8, 2015.)

The most active focus of reforms in 2016 will be focused on some of the next-generation edges of the medtech space, in particular: combination products, molecular diagnostics and digital health.

Both industry and FDA have reached the conclusion that current regulatory pathways do not work well for products that include both a device and a drug (or biologic), and it appears increasingly likely that a new combination-product pathway will be debated in 2016 and passed in 2017 as part of user-fee reforms. (See “2016 Will Be A Big Year For Combo Product Reform, FDA Says” — “The Gray Sheet,” December 29, 2015.)

On diagnostics, FDA is getting set in 2016 to issue its final policy to start actively regulating laboratory-developed tests (those that are made and performed as a clinical diagnostic service in the same lab) similar to how the agency regulates in vitro diagnostic test kits. Laboratories remain opposed to the plan, while IVD kit makers welcome a policy that will establish a more level regulatory playing field for all diagnostics. One ultimate possible outcome: Congress could establish a completely new regulatory paradigm for all diagnostics in the US, leveraging proposals that have already been circulated by clinical and industry collaborators.

Meanwhile, FDA has settled into what it feels is the right approach for digital and mhealth that puts more focus on apps and high-risk digital tools.

“FDA has settled into an approach for digital and mhealth that puts more focus on apps and high-risk digital tools.”

By David Filmore
R&D. Its 2016 list unusually errs away from new medtech solutions, but still shows a medtech R&D base with the sharpest of cutting edges: catheter-delivered neurovascular stent retrievers to remove blood clots in stroke victims; frictionless remote monitoring of glucose levels via a skin-top biosensor that measures insulin and reports the results to both the diabetic patient and the doctor; protein biomarker analysis cancer screening, for real-time information on cancer presence that allows for greater accuracy and earlier detection; and safer and cheaper “brain-machine interfaces” that take forward advances in neural signal research and bring the prospect of brain-powered prosthetics nearer.

Elsewhere, Forbes says that next-generation wearables will become a $6 billion market in 2016, and the technologies will evolve from primarily monitoring to providing therapeutic support, and as a result health care and consumer technology companies will be on the hunt for strategic acquisitions of early-stage wearables companies. A 2015 survey done by IMS found that almost half of consumers polled said they would consider using wearables in the near future. Crucially, the question is how to pay for the benefits of, say, additive manufacturing – 3-D printed biomedical products that could be manufactured near the point-of-care solutions? Will these be confined to niche usage, or does the technology offer a plausible option for the wider health care system?

AN INDUSTRY IN TRANSFORMATION IN 2016

The industry and the climate it works in have changed. The squeeze on the medtech industry still comes from all sides – patients, payers and providers – and revenues and margins remain under pressure, even though the wider economic crisis years that followed the collapse of Lehman Brothers are in the past.

But the costs of doing business, of regulatory requirements and of market access generally have probably never been higher for medtechs, and the outlook is set to remain challenging, with developed markets showing only low-to mid-single digit growth in the coming years while manufacturers also embrace the challenges posed by fast-evolving digital health care.

At the same time the industry is expected to play a full part in transforming health care by introducing medtech innovations and championing innovative, partnership-based market approaches across the medtech value chain, and decision-makers are focusing more sharply on products that are part of the value-based health care approach. This will be the challenging environment for modern medtech in 2016.
Pharma’s Love Affair With Dealmaking: No End In Sight

The pace of pharma dealmaking continued unabated in 2015, climaxing with Pfizer’s agreed $160 billion merger with Allergan. Conditions are right for this situation to persist, at least for the foreseeable future.

BY PETER CHARLISH

Growing shareholder expectations, historically low interest rates and a new generation of company executives with a financial services background are continuing to drive dealmaking in the pharmaceutical sector.

This constant stream of M&A activity has led to an exodus of executives from big phamas to biotechs.

Pricing continues to be a thorny issue, with more big-ticket launches and even the prices of generics creeping up, although to some extent this may be offset by the appearance of the first biosimilars in the US.

Drug pipelines are full and last year also saw a steady flow of innovative new products, notably in the oncology and orphan disease areas.

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tax issues, which the abortive attempt to acquire AstraZeneca a year earlier had left unresolved. Pfizer has a large cash reserve outside the US, which it is reluctant to repatriate because of the high rate of tax it would attract.

There were few surprises therefore when in November Pfizer announced an agreed $160 billion merger with Allergan, the third biggest corporate deal ever and by far the biggest in the healthcare sector. Pfizer denied that the deal was being done simply as a means of lowering its effective tax rate and, to be fair, the US authorities had acted in 2014 to make such “tax inversion” deals far less attractive. Nevertheless, the deal will be executed as a merger in which Dublin, Ireland-domiciled Allergan will become the parent company, although the combined group will be called Pfizer. Pfizer has indicated that the deal would lead to its having an effective tax rate in 2017 onwards of about 17% to 18%, in contrast to its current 25%.

Of course, there are other business reasons for the merger. It will give Pfizer the critical mass it needs to separate its established and innovative products businesses, something that it has been working toward for some years (see “Pfizer/Allergan: Breaking Up Is Hard To Do (Unless There’s A New Tax Law)” — “The Pink Sheet,” November 30, 2015), whereas Allergan will get direct access to some 70 geographic markets where it currently has no presence, plus another 30 where it presently operates through distributors. But these reasons haven’t stopped politicians from both sides of the political divide from condemning the deal.

The tax advantage of acquiring or merging with a company in a relatively low-tax jurisdiction is not the only factor driving biopharma M&A activity. Other dynamics at play include historically low borrowing rates, making such deals more affordable, together with apprehension that interest rates will have to rise sooner or later (we have already seen the Federal Reserve lift US rates by 0.25 percentage points in December); broad expertise in M&A transactions, as many financial services personnel with M&A experience moved out of the banking sector into industry following the financial crisis; and growing shareholder expectations that can more easily be met via an acquisition than by organic growth.

As none of these drivers is likely to go away at least for the time being, the current level of M&A activity is likely to continue for the foreseeable future. A recent survey by McKinsey, for example, found that 86% of respondents in the health care sector thought that the number of M&A deals in the next 12 months would be at least as high as in the previous 12 months. Look for more about the McKinsey survey in an upcoming issue of IN VIVO.

One notable offshoot of this constant stream of M&A activity and other bubble-driven market factors: the exodus of executives from big pharma. By our count, close to 20 execs have abandoned their posts for biotech gigs in the past year or so. (See Exhibit 1.)

The reasons behind this trend — if it is a trend — of sweeping execs away from big pharma job security, pay and perks into tiny biotechs are readily apparent. The huge influx of fresh capital into biotech reflects increased confidence in biomedical advances leading to new products, and it has bolstered prospects for building a biotech for the long haul generally needed to discover and develop commercializable assets. Significant scientific advances can be leveraged most dynamically in smaller companies and the capital base has expanded with ample resources to support innovation.

There are cultural and personal drivers as well. As Jeremy Levin, PhD, the former president and CEO of Teva, now CEO of Ovid Therapeutics, pointed out in July’s START-UP, talented leaders see limits to their ability to make an impact in large corporate settings and long for a more dynamic environment. (See “Big Pharma’s Executive Brain Drain Benefits Biotech” — START-UP, June 2015.)

**THE PRICING HAS TO BE RIGHT**

Drug pricing is another issue that seems to hit the headlines every year, and 2015 was no exception. For weeks, the saga of Martin Shkreli and Turing Pharmaceuticals AG dominated trade and popular media outlets. Turing, a biotech that focuses on unmet medical needs, acquired US commercial rights to toxoplasmosis drug Daraprim (pyrimethamine), and promptly increased the price from $13.50 to $750 per dose (an increase of 5,456%).

Turing was not the first company to raise the price of a drug above what many regard as reasonable: Amedra Pharmaceuticals LLC did a similar thing in 2013, for example, when it raised the price of the anthelmintic albendazole from around $6 per day to almost $120 per day. Valeant too has come under fire from Congress and the media in recent months for raising prices for the cardiovascular drugs Nitropress (sodium nitroprusside) and Isuprel (isoproterenol) by 212% and 525%, respectively, after purchasing the rights to the products from Marathon Pharmaceuticals LLC. (See “PhRMA Takes Aim At Valeant In Defense Of Drug Pricing By ‘Innovative’ Firms” — “The Pink Sheet,” October 26, 2015.) And an article in JAMA Dermatology last November highlighted how two products sold by Valeant for treating cancer-related skin conditions had increased in price by around 1,700% over the previous six years: the drugstore price of Tarce (bexarotene) gel, indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma, rose to $30,320 in 2015, compared with $1,687 in 2009, whereas the price of Carac (fluorouracil) cream, used for the treatment of multiple actinic or solar keratoses, was $2,865 last summer, compared with $159 in 2009. Valeant pointed out that the retail prices cited in the study rarely represent the prices that patients and insurers actually pay, and that alternative generic products are available.

To be sure, most of these are old drugs that have long since gone off patent. In the past, the loss of patent protection on a drug molecule has usually opened the door to generic competition, thus effectively reining in prices. But, as those present at a hearing convened by the House Democratic Steering and Policy Committee at the end of the year heard, the dynamics of the generics industry are changing, with widespread consolidation and some manufacturers almost as big as traditional “big pharma” companies. The result has been less competition for some older medicines, and some companies gaining a virtual monopoly in their particular area. Inevitably, this has led to prices creeping up.

For new drugs, nearly all of the increase in medical spending is due to the rising cost of specialty drugs. Of course, manufacturers in the US are able to set their own prices which, as a result, tend to increase over time. This is true either when one considers individual products or drug prices in general. In response, payers are forced to manage
their formularies more aggressively. Many providers, a number of whom, under provisions of the 2010 Affordable Care Act, are paid by results, are forced to determine the most cost-effective treatment pathways. The challenge here for pharma: set price points that payers can tolerate. (See “The Shrinking Value Of Best-In-Class And First-In-Class Drugs” — IN VIVO, July 2015.)

Both the White House and a Congressional committee are currently looking at the issue of drug pricing. But laws won’t change fast, if they change at all. Hence a handful of organizations and companies are stepping in to try to make choice of therapy easier, by providing transparent, comparative information about the efficacy, drawbacks and costs of a range of treatment options. (See “Scoring Value: New Tools Challenge Pharma’s US Pricing Bonanza” — IN VIVO, October 2015.)

New pricing models are emerging. Some payers are negotiating performance-related risk-sharing contracts with drug manufacturers. Under such arrangements, drug prices are related to the achievement of pre-agreed outcomes. In addition, contracts may include guarantees that drug use will be restricted to certain groups of patients, while in return payers may offer preferred formulary status to specific products. Outcomes-based contracts for drugs have been rare in the US, but some companies have been quite aggressive in pursuing them. Amgen, for instance, achieved preferred status for its PCSK9 inhibitor Repatha on two payer formularies in 2015: Harvard Pilgrim and CVS Health Corp. (See “Amgen’s Repatha Pricing Deal With Harvard Pilgrim Hinges On Results, Utilization” — “The Pink Sheet” DAILY, November 9, 2015 and “Amgen’s Repatha Gets Big Formulary Win With CVS Health” — “The Pink Sheet” DAILY, November 23, 2015.) Another product that has been mooted as appropriate for such an agreement is Novartis AG’s heart failure treatment Entresto (sacubitril plus valsartan), although to date none has been announced. In general, experience with such contracts has been relatively limited, not least because there has been lack of agreement over how to measure effectiveness and who precisely should measure it.

Another stumbling block has been the fact that Medicaid, one of the largest payers in the US, uses a different payment

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**Exhibit 1**

**Pharma Execs On The Move To Biotech**

<table>
<thead>
<tr>
<th>EXECUTIVE AND NEW BIOTECH</th>
<th>FORMER PHARMA POSITION</th>
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<tbody>
<tr>
<td>Detlev Biniszkiewicz, PhD, President &amp; CEO, Surface Oncology</td>
<td>VP, Oncology Strategy, AstraZeneca</td>
</tr>
<tr>
<td>Tony Coles, Co-founder and CEO, Yumanity Therapeutics</td>
<td>CEO, Onyx Pharmaceuticals</td>
</tr>
<tr>
<td>Ron Cooper, President &amp; CEO, Albireo AB</td>
<td>President, Europe, Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Vlad Coric, PhD, Biohaven Pharmaceutical Holding Co.</td>
<td>Neuro-Oncology Indication Lead, Immuno-Oncology, Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Jose-Carlos Gutiérrez-Ramos, CEO, Synlogic</td>
<td>SVP, Global Head of BioTherapeutics Research, Pfizer</td>
</tr>
<tr>
<td>Annalisa Jenkins, CEO, Dimension Therapeutics</td>
<td>SVP, Head of Global Research and Development, Merck Serono</td>
</tr>
<tr>
<td>Jeremy Levin, CEO, Ovid Therapeutics</td>
<td>CEO, Teva Pharmaceuticals</td>
</tr>
<tr>
<td>Arthur Levinson, PhD, CEO, Calico Life Sciences LLC</td>
<td>CEO, Genentech</td>
</tr>
<tr>
<td>Neil McDonnell, PhD, CEO, Metacrine Inc.</td>
<td>SVP, CV &amp; Metabolic Diseases, Takeda Pharmaceuticals USA</td>
</tr>
<tr>
<td>Briggs Morrison, CEO, Syndax Pharmaceuticals</td>
<td>EVP, Global Medicines Development &amp; CMO, AstraZeneca</td>
</tr>
<tr>
<td>Paolo Paoletti, CEO, Kesios Therapeutics</td>
<td>President, GSK Oncology</td>
</tr>
<tr>
<td>Roger Pomerantz, CEO, Seres Therapeutics</td>
<td>Worldwide Head, Licensing &amp; Acquisitions, EVP, Merck &amp; Co.</td>
</tr>
<tr>
<td>Anna Protopapas, CEO, Mersana Therapeutics</td>
<td>President, Millennium–Takeda Oncology, EVP, Global Business Development, Takeda Pharmaceuticals</td>
</tr>
<tr>
<td>Jill Schiaparelli, CEO, President &amp; CEO, Intelemed</td>
<td>Chief Marketing Officer, AxoGen</td>
</tr>
<tr>
<td>Chris Viehbacher, Managing Partner, Gurnet Point Capital; Chairman, Boston Pharmaceuticals</td>
<td>CEO, Sanofi</td>
</tr>
<tr>
<td>James Ward-Lilley, CEO, Vectura Group</td>
<td>VP, Respiratory, Inflammation &amp; Autoimmunity, AstraZeneca</td>
</tr>
<tr>
<td>Charles Wilson, Co-founder &amp; CEO, Unum Therapeutics</td>
<td>VP, Global Head, Strategic Alliances, Novartis</td>
</tr>
</tbody>
</table>

**SOURCES:** Strategic Transactions; Company reports
model than most commercial payers, one that is not amenable to these risk-sharing arrangements. However, there are signs of change on the way: the Centers for Medicare and Medicaid Services is reported to be in discussions with manufacturers about how such arrangements could be reconciled with Medicaid’s payment system.

**BIOSIMILARS DAM IS BREACHED**

If the price of generic versions of conventional small-molecule drugs is creeping up, there is better news for payers in the biologics area. Following the approval of the first US biosimilar product, Sandoz Inc.’s Zarxio (filgrastim-sndz), in March, a stream of biosimilar approvals is expected, many of them via the new 351(k) regulatory route. Prices of biosimilars are expected to be between 20% and 35% lower than those of originator products.

Zarxio is a biosimilar version of Amgen’s human granulocyte colony-stimulating factor Neupogen, and its journey onto the US market has not been an easy one. Even before Zarxio was approved, Amgen filed a lawsuit alleging that Sandoz had violated the requirements for disclosure and negotiation procedures – the so-called patent dance – contained in the Biologics Price Competition and Innovation Act (BPCI Act), the law that created the regulatory pathway for biosimilars.

After a number of court hearings and considerable legal wrangling between the parties, the US Court of Appeals for the Federal Circuit finally ruled in July that, as BPCI Act requires biosimilar companies to give the manufacturer of the originator biologic 180 days' notice of their intention to market the copy, Sandoz should wait 180 days from the date of approval before launching Zarxio. The court also ruled against Sandoz by stating that the 180 days' notice can only be given once approval has been granted. However, the case didn’t all go Amgen’s way: the court additionally ruled that engaging in the patent dance was not mandatory, a ruling with potentially far-reaching implications. (See “Biosimilar Sponsors Can Avoid Patent Dance, But Innovators Win Extra Exclusivity” — “The Pink Sheet” DAILY, July 21, 2015.)

Zarxio finally reached the US market at the beginning of September 2015, at a 15% discount from the price of Neupogen. The FDA has stressed that, although its biological properties are highly similar to those of Neupogen, the two products are not interchangeable, and pharmacists are not permitted to substitute Zarxio if a physician prescribes Neupogen.

Zarxio’s legal struggles aside, the future for biosimilars in the US is not assured, according to FDA Center for Drug Evaluation and Research (CDER) director Janet Woodcock. Speaking in November, she said that when generic small-molecule drugs first appeared they were treated with some suspicion, and their uptake by clinicians was slow, and the situation with biosimilars is likely to be very similar. In Europe, where biosimilars have been on the market rather longer than in the US, uptake has also been slow and varies from country to country.

Nevertheless, the dam has now been breached, and the FDA is currently considering approval applications for a number of other biosimilars. They include Amgen’s
Biopharmaceuticals

ABP-501, a biosimilar of AbbVie Inc.’s Humira (adalimumab); Sandoz’s pegfilgrastim, a biosimilar of Amgen’s Neulasta; and Sandoz’s GP-2015, a biosimilar of Amgen’s Enbrel (etanercept).

THE PIPELINE PICTURE

It was another stellar year for pharma pipelines. According to our colleagues at Citeline, the total number of drugs in development stands at 13,718. That’s up 11.5% from 2014, and continues a 16-year upward trend. (See Exhibit 2.)

So it appears that pipeline expansion is continuing and even accelerating – along, presumably, with the inevitable concomitant increase in R&D spending.

Or maybe not. Concerns by companies about their ability to achieve high prices for new products, as discussed earlier, together with the ever-increasing cost of bringing products to market, are starting to have an impact on R&D activities, according to a recent analysis by professional services firm Deloitte. The situation is exacerbated by the slow trend toward personalized medicine, which has led to a fall in peak sales forecasts for new products. The net result is that R&D returns among major life science companies are at their lowest for five years, Deloitte says.

Despite these warnings, however, the level of innovation by the pharma industry continues to be high: the FDA approved

Exhibit 3

High-Value IO Alliances (>500m), 2015

<table>
<thead>
<tr>
<th>DATE</th>
<th>DEAL</th>
<th>POTENTIAL VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2015</td>
<td>Novartis Institute for BioMedical Research acquires extra-US rights to Aduro Biotech’s preclinical cyclic dinucleotides, which stimulate the Stimulator of Interferon Genes (STING) pathway and thus inhibit tumor cell growth.</td>
<td>$750m</td>
</tr>
<tr>
<td>April 2015</td>
<td>Roche obtains exclusive license to Curadev Pharma’s preclinical indoleamine 2,3-dioxygenase (IDO1) and tryptophan 2,3-dioxygenase (TDO) immune checkpoint inhibitors, which may be used as either monotherapies or in combination with a Roche oncology drug.</td>
<td>$555m</td>
</tr>
<tr>
<td>April 2015</td>
<td>AstraZeneca/MedImmune licenses exclusive global rights to develop and sell a cancer therapy combining AstraZeneca’s MEDI-4736 with Innate Pharma’s IPH2201. A2 also gets access to IPH2201 as a monotherapy and combination treatment in other undisclosed areas.</td>
<td>$1.2bn</td>
</tr>
<tr>
<td>June 2015</td>
<td>Celgene and Juno Therapeutics enter a 10-year alliance with an initial focus on T-cell receptor- and chimeric antigen receptor T-cell (CART)-based treatments for cancer and autoimmune diseases.</td>
<td>$1.1bn</td>
</tr>
<tr>
<td>July 2015</td>
<td>Regeneron Pharmaceuticals and Sanofi enter a drug development deal focusing on PD-1 and other immuno-oncology antibodies over a period of five years (with the possibility of a three-year extension).</td>
<td>$2.7bn</td>
</tr>
<tr>
<td>Sept. 2015</td>
<td>Celgene and Nurix collaborate exclusively on the development of small-molecule therapies targeting the ubiquitin proteasome system. Potential applications include for cancer, inflammation, immunology and immuno-oncology.</td>
<td>$555m</td>
</tr>
<tr>
<td>Sept. 2015</td>
<td>Jiangsu Hengrui Medicine grants Incyte exclusive global (except mainland China, Hong Kong, Macau and Taiwan) development and commercialization rights to its preclinical anti-PD-1 Mab, SHR-1210.</td>
<td>$615m</td>
</tr>
<tr>
<td>Oct. 2015</td>
<td>Alpine Immune Sciences grants Kite Pharma exclusive global rights to its transmembrane immunomodulatory protein (TIP) technology and two associated cancer immunotherapy programs, which Kite will further develop into chimeric antigen receptor (CAR) and T-cell receptor (TCR) drug candidates.</td>
<td>$535m</td>
</tr>
<tr>
<td>Oct. 2015</td>
<td>Bristol-Myers Squibb acquires exclusive global rights to develop and sell Five Prime Therapeutics’ Phase I colony stimulating factor 1 receptor inhibitor antibody FPA-008 for immuno-oncology indications. The agreement covers all modifications, derivatives, fragments or variants of anti-CSFR1 antibodies, and replaces a deal signed in March 2014.</td>
<td>$1.7bn</td>
</tr>
<tr>
<td>Dec. 2015</td>
<td>Roche partners with SQZ Biotechnologies to modify B-cells and trigger an immune-mounted cascade to treat several types of cancer.</td>
<td>$500m</td>
</tr>
</tbody>
</table>

SOURCE: Strategic Transactions
45 new molecular entities and new therapeutic biological products in 2015, slightly more than in the previous year and one of the highest totals ever. (See “Big Pharma’s Winning Formula: Many Approvals, Narrow Markets” — “The Pink Sheet,” January 4, 2016 and sidebar, “2015 Standout Approvals.”)

**ONCOLOGY STILL ATTRACTS MOST INVESTMENT**

For investors, oncology is still the most attractive target. In 2015, the number of initial public offerings and private financings for cancer-focused biopharmas was 33% more than the next biggest area, neurology. (See “2015’s Top Biopharma Dealmakers,” this issue.)

Those two areas also topped alliances in 2015. The year saw a high level of collaborative deals forged in oncology, and particularly in immuno-oncology. (See Exhibit 3.) Two in particular stand out, for their monetary value apart from anything else. In June, Celgene Corp. and Juno Therapeutics Inc. announced a 10-year collaboration to advance potentially groundbreaking immunotherapies for patients with cancer and autoimmune diseases. Celgene made an initial payment of roughly $1 billion, which includes the purchase of around 9.1 million shares of Juno stock, with the option to increase its stake over time. The deal gave Celgene the option to be the commercialization partner for Juno’s oncology and cell therapy autoimmune product candidates, including Juno’s CD19 and CD22 directed CAR-T product candidates.

The following month, Sanofi and Regeneron Pharmaceuticals Inc. entered into a global collaboration to discover, develop and commercialize new treatments in the field of immuno-oncology. As part of the agreement, the two companies will jointly develop a programmed cell death protein 1 inhibitor that is currently in Phase I and plan to initiate clinical trials in 2016 with further new therapeutic candidates. That deal included a $640 million initial payment from Sanofi and an investment of $1 billion (25% Regeneron, 75% Sanofi) for discovery through proof-of-concept development (usually a Phase IIa study) of monotherapy and novel combinations of immuno-oncology antibody candidates.

**AND WHAT OF 2016?**

As expected, the level of dealmaking is expected to continue at at least the same level as in 2015, and a number of new biosimilars will reach the market. Other innovative new products expected to be launched in the US in the coming weeks and months include: Eli Lilly & Co.’s Portrazza (necitumumab), for the treatment of advanced squamous non-small cell lung cancer; Genmab’s Darzalex (daratumumab), for the treatment of multiple myeloma; and United Therapeutics Corp.’s Novanastase for the treatment of neuroblastoma.

Drug pricing issues will continue to tax minds, as part of the wider problem of how to control spending on health care. Expect to see more innovations in the way pharmaceuticals and other advanced treatments are paid for. And with the US presidential election process gaining momentum, expect the whole issue of health care to get a lot more political.

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Diagnostics In 2015: Past Trends Coalesce, New Roads Open

The introduction of Apple’s ResearchKit is our top story of the year. Mobile apps and the increasing ability to take measurements of vital signs, gather information on habits and collect other phenotypic measures is rapidly changing thinking about clinical trials design.

The introduction of Apple’s ResearchKit is our top story of the year. It heralds the ascendance of mobile apps and the influence of digital health and analytics.

The ability to take measurements of vital signs, gather information on habits and collect other phenotypic measures is rapidly changing thinking about clinical trials design.

Roche, the market leader in molecular diagnostics, was highly visible on the dealmaking front in 2015. Its most prominent transaction came early: in January, it invested more than $1.16 billion in tumor profiling services organization Foundation Medicine.

Roche’s deals attest to two trends heightened in 2015: multiple firms making large bets on liquid biopsy, and increased interest in infectious disease diagnostics.

BY MARK RATNER

Many of the fundamental trends and issues we’ve spotted in the past several years – the degree of leverage the diagnostics industry can gain from the integration of companion diagnostics into pharma’s development planning, the regulation of laboratory-developed tests, and the infiltration of next-generation genome sequencing on just about every level of drug/diagnostics development, for example – coalesced in 2015, much as they had started to do last year when we titled our year-in-review piece “More of the Same.” (See “Diagnostics In 2014: More Of The Same” — IN VIVO, January 2015.) This past year may be thought of as one of acceptance, or consolidation of thought. These matters are now well-trod turf. But much new territory was also claimed during the year, most notably in the areas of digital health, data acquisition and analytics.

Call it the ascendance of the app, and no story carries more weight than the introduction of Apple’s ResearchKit, announced in March and made available to developers a month later. The ResearchKit is an open-source software framework that allows researchers and developers to create apps to gather patient data for studies more frequently and accurately. It’s being used by leading academic institutions to study and diagnose major diseases including Stanford University School of Medicine (heart health), the Icahn School of Medicine (asthma), Duke University (autism), Johns Hopkins University (epilepsy), Yale School of Medicine (cardiomyopathies), Massachusetts General Hospital (diabetes) and Oregon Health & Science University (melanoma). The ability to take measurements of vital signs, gather information on habits and collect other phenotypic measures is rapidly changing thinking about clinical trials design.

Major pharma are already using apps to monitor patients’ progress in trials: Roche, for example, is giving participants in a Phase I trial in Parkinson’s disease a smartphone loaded with an app that will test them in a variety of daily activities and measure hand tremor. (Sage Networks pioneered this concept with its Parkinson mPower app, one of the first ResearchKit offerings; Sage also had a large hand in another app, “Share the Journey,” which tracks fatigue, mood, cognitive changes, sleep disturbance and reduction in exercise in breast cancer patients.) Medidata Solutions Inc. has linked the ResearchKit with its cloud-based...
clinical research analysis capabilities. Dozens of clinical trials are already using apps to monitor participants in trials.

That said, the infusion of the high-tech mind-set into the tightly regulated health care industry can potentially cause problems, as when the Federal Trade Commission challenged several marketers for deceptively claiming their mobile apps could detect symptoms of melanoma, even in its early stages. In one case, a final order barred Health Discovery Corp. from making such claims. (See "Industry Roundup: FDA Investigation Prompts Criminal Charges Against Supplement Marketer" — "The Tan Sheet," April 20, 2015.) It stresses me to think that you have hundreds of thousands of developers trying to build research apps, who’ve never gone through human subjects training and don’t know what an institutional review board is,” says John Wilbanks, PhD, chief commons officer at Sage Networks.

On the other hand, 2015 marked the return of 23andMe Inc., to the health care market, validating the ability of industry and regulators to work together to protect consumers. On October 21, it launched a new Personal Genome Service For Carrier Screening After Work With FDA” — “The Gray Sheet,” October 21, 2015.) Roche, the market leader in molecular diagnostics, was highly visible on the deal-making front in 2015. Its most prominent transaction came early: in January, it took the majority stake in Foundation Medicine Inc. and also established a five-year R&D collaboration in which the companies will advance multiple programs. In all, Roche is investing more than $1.16 billion in the tumor profiling services organization, including $74 million for programs focused on cancer immunotherapy testing, circulating tumor DNA (liquid biopsy), continuous blood-based monitoring and companion diagnostics. At least for now, the deal with Roche is centered in Roche’s pharma division, raising the question of whether Foundation Medicine could become captive to Roche’s internal drug development interests. (See “Which Path Forward For Foundation Medicine?” — IN VIVO, June 2015.) The Roche/Foundation Medicine deal and a much smaller one ($2 million up front) between T2 Biosystems Inc. and Canon US Life Sciences Inc. to develop a Lyme disease diagnostic were the only alliances with designated up-front deal values – a departure from 2014.

The following month, Roche bought Signature Diagnostics AG, which has biobanks that provide the basis for development of circulating cell-free DNA tests in colorectal, lung and other cancer types. It also acquired CAPP Medical, which uses next-generation sequencing to detect, isolate and quantify circulating tumor DNA in blood with clinical potential in cancer drug selection and tumor monitoring, in 2015, as well as another next-gen sequencing specialist, Kapa Biosystems Inc. Also, Roche Molecular Diagnostics paid $190 million up front for private microbiology diagnostics company GeneWEAVE BioSciences Inc. That deal brings Roche technology for rapidly detecting multi-drug resistant organisms in clinical samples and analyzing antibiotic susceptibility or resistance, presumably with an eye to developing companion diagnostics for use with its portfolio of antibiotics. Roche’s deals attest to two trends heightened in 2015: multiple firms making large bets on liquid biopsy, and increased interest in infectious disease diagnostics. (See Exhibit 1.)

A slew of liquid biopsy-related announcements ushered in the year. (See “Liquid Biopsy News: Qiagen CE Mark, Foundation-Roche Deal And More” — “The Gray Sheet,” January 26, 2015.) On January 12, Qiagen NV gained a CE mark for a companion diagnostic that analyzes circulating tumor DNA in blood, to be used in patients with non-small cell lung cancer to identify which of them could ben-

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**Exhibit 1**

**Selected Diagnostics Acquisitions Of 2015**

<table>
<thead>
<tr>
<th>ACQUIRER</th>
<th>COMPANY ACQUIRED</th>
<th>UP-FRONT DEAL VALUE</th>
<th>MONTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opko</td>
<td>Bio-Reference Laboratories</td>
<td>$1.6bn</td>
<td>June</td>
</tr>
<tr>
<td>Neogenomics</td>
<td>GE Healthcare’s Clariant</td>
<td>$277m plus stock</td>
<td>Oct.</td>
</tr>
<tr>
<td>Roche Molecular Diagnostics</td>
<td>GeneWEAVE</td>
<td>$190m</td>
<td>Aug.</td>
</tr>
<tr>
<td>Alere</td>
<td>US Diagnostics</td>
<td>$60m</td>
<td>July</td>
</tr>
<tr>
<td>True Health</td>
<td>Health Diagnostics Laboratory</td>
<td>$37.1m through a bankruptcy auction</td>
<td>Sept.</td>
</tr>
<tr>
<td>Cancer Genetics</td>
<td>Response Genetics</td>
<td>$7m plus stock</td>
<td>Aug.</td>
</tr>
<tr>
<td>OpGen</td>
<td>AdvanDx</td>
<td>$2.43m</td>
<td>July</td>
</tr>
</tbody>
</table>

SOURCE: Strategic Transactions
benefit from treatment with AstraZeneca PLC’s EGFR mutation-targeting Iressa (gefitinib) – the result of a collaboration that began in 2009 with DxS, which Qiagen acquired later that year and renamed Qiagen Manchester. Biocent Laboratories Inc. also launched an EGFR mutation test on January 12 using its liquid biopsy platform. A day later, Thermo Fisher Scientific Inc. announced a deal for the right to distribute Cynvenio Biosystems Inc.’s liquid biopsy platform. Then on January 15, Sequenom Inc. told investors at the JP Morgan Health Care Conference of its plans to launch a liquid biopsy test.

Investors responded to these developments. Biocept netted $9.4 million in a follow-on offering in February, as did Trovagene Inc., which raised $21.4 million, followed by a $37.6 million offering six months later. Privately held Guardant Health Inc. raised $50 million in a Series C round in February to expand the availability of its blood-based cancer test. Next-gen sequencer HTG Molecular Diagnostics Inc. went public in May 2015, partly on the strength of claims that its platform is compatible with detection of cell-free circulating nucleic acids.

Genomic Health Inc. also announced in May its plans to shift R&D efforts toward a liquid biopsy platform. Then in June, Laboratory Corp. of America Holdings got in the game via a deal with Sysmex Corp.’s molecular diagnostics unit, Sysmex Inostics GMBH, to create tests for clinical trials of cancer drugs using Sysmex’s liquid biopsy platform.

Roche/GeneWeAVE, OpGen Inc.’s IPO and subsequent purchase of AdvanDx Inc. and progress made by competitors Accelerate Diagnostics Inc., which is developing a fluorescent in situ hybridization-based system, and Biofire Diagnostics LLC, the US molecular diagnostics affiliate of bioMérieux SA using PCR amplification, all helped bring the development of infectious disease diagnostics into greater relief. Roche is also developing targeted antibiotics, suggesting a possible use for the GeneWeAVE system as an eventual “rule-in” companion diagnostic test for its drugs. But the others are pure plays, competing with the likes of Cepheid, Nanosphere Inc. and Genmark Diagnostics Inc. In December, bioMérieux and Illumina announced the launch of a service for the epidemiological monitoring and control of health care-related infections in hospitals, using next-gen sequencing. It is the first offering derived from a 2014 collaboration combining the companies’ respective strengths in microbiology and sequencing. (See “bioMérieux, Illumina to Develop Sequencing Products for Hospitals” — “The Gray Sheet,” November 18, 2014.)

And then there was the turmoil around Theranos Inc., our one-off story for 2015. After years of rumors and questions about the substance of its claims to be able to multiplex dozens of lab tests at low cost using only a few drops of blood, and with the company insistently cloaked in secrecy, IN VIVO embarked on a story right before FDA cleared its herpes simplex test in July. Our best sources’ comments, all on background, ranged from “They have been really impressive with their stealth approach.” to “For now, we have not seen any financials for Theranos. So all they are doing for now is spoiling the market price of tests.” One VC had come away from meetings with Theranos a few years back “unimpressed.” The story didn’t run, however, as Theranos backed off an interview and partners we contacted went silent. Then in October, The Wall Street Journal accused the company of not using its own technology to run most of its tests. A week later, WSJ reported that Theranos’ key distribution partner, Walgreen’s, had called a halt to any expansion plans. Safeway pulled the plug on a deal in early November, according to WSJ. Just before that, FDA confirmed it had cited the company for selling its Nanotainer blood specimen device without 510(k) clearance, and for quality system violations.

Comments: Email the editor: Nancy.Dvorin@informa.com

Related Reading

“Diagnostics In 2014: More Of The Same” — IN VIVO January 2015 [A#201500014]


“23andMe Launches Personal Genome Service For Carrier Screening After Work With FDA” — “The Gray Sheet,” October 21, 2015 [A#01151026011]

“Which Path Forward For Foundation Medicine?” — IN VIVO June 2015 [A#201500100]


“bioMérieux, Illumina to Develop Sequencing Products for Hospitals” — “The Gray Sheet,” November 18, 2014 [A#01141124006]
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TG Therapeutics Builds A Business Model For Today

The speed with which TG Therapeutics burst on the scene, along with the impressive potency and safety of its novel combinations of cancer drugs, has perhaps blinded observers to the unique business model that has carried it this far.

BY MICHAEL GOODMAN

Cancer specialist TG Therapeutics Inc. has recently shown positive mid-stage data for its assets, both alone and in combination, in patients with advanced B-cell cancers. The speed with which it burst on the scene, combined with the potency and safety of its drugs, has perhaps blinded observers to the unique business model that has carried it this far.

The main element in the model is TG’s dedication from the start to proprietary combinations of its own drugs. TG understood that owning its pipeline would satisfy several key challenges facing biopharmas in the age of combination therapy.

It would allow the company to control the design and conduct of complex trials involving combinations or sequencing of two or more drugs. It would obviate the need to negotiate involved IP and logistical arrangements with big pharma. TG would be able to keep the lion’s share of revenue should its drugs reach market, and it would give TG sole discretion over pricing. That last benefit addresses the pressure that companies, increasingly cancer companies, come under to price their drugs responsibly. Moreover, it flies in the face of current wisdom that says combinations of cancer drugs are necessarily expensive.

Other elements of TG’s model – the avoidance of R&D partnerships and an unprecedented emphasis on the safety of its assets – solve other challenges that small, young companies face. For instance, that combinations of drugs are not only more expensive, but also necessarily more toxic. Or the market wisdom that says that tie-ups with big pharma are validating, value-adding events.

TG Therapeutics was spun out from France-based LFB Biotechnologies SAS in 2010. In April 2011 it took an option from LFB to license rights to ublituximab, a next-generation, glycoengineered, chimeric CD20 antibody. In late 2011, TG reverse merged with Manhattan Pharmaceuticals, and soon after raised $25 million in a private placement and exercised its option to ublituximab (TG-1101).

CEO Michael Weiss, former CEO of Keryx Pharmaceuticals, lost no time in licensing in other assets to combine with ublituximab. In August 2012, TG paid an undisclosed up-front to Swiss-based...
Rhizen Pharmaceuticals SA to develop its preclinical PI3K delta inhibitor to Phase II, after which it exercised an option for full global rights to the compound, now known as TG-1202. It struck again in June 2014, issuing $125,000 of its common shares as an up-front for a global license to an IRAK4 inhibitor program from Ligand Pharmaceuticals Inc. And in March 2015, it licensed in a PD-L1 and a glucocorticoid-induced tumor necrosis factor receptor (GITR) antibody from Checkpoint Therapeutics Inc., a subsidiary company of Fortress Biotech Inc., for $500,000 up front. The checkpoint inhibitors originated in the lab of Wayne Marasco, MD, PhD, of the Dana-Farber Cancer Institute.

TG’s assets are distinguished by their efficacy and safety profiles and by their complementary mechanisms that allow them to be used in various combinations. The combination of 1101 and 1202, which TG refers to as 1303, is the backbone for further combinations in hematologic cancers and, soon, in autoimmune diseases.

1303 is currently in the Phase III UNITY-CLL trial, under SPA agreement with FDA, where patients are randomized into four arms (1101, 1202, 1303 and standard-of-care) to demonstrate the contribution of each agent to the 1303 combination and to demonstrate progression-free survival (PFS) over Roche’s Gazyva (obinutuzumab) and chlorambucil, a standard treatment for advanced chronic lymphocytic leukemia (CLL).

The 1303 backbone figures in another trial, this one at the University of Pennsylvania’s Abramson Cancer Center, the Phase I/Ii trial of 1101, 1202 and Merck & Co. Inc.’s PD-1 inhibitor Keytruda (pembrolizumab) in patients with relapsed or refractory CLL. Moreover, 1303 will likely serve as a backbone in TG’s first foray into autoimmune disease; the company plans to start a Phase I/Ii trial in multiple sclerosis in 2016.

TG’s lead program is the Phase III GENUINE trial of 1101 plus ibritinib in patients with previously treated, high-risk, chronic CLL. The trial is targeting the end of 2016 to analyze the overall response endpoint; if positive, the company will file for accelerated approval under SPA.

THE ERA OF THE COMBINATION

Combination therapy has been a mainstay in HIV and HCV for several decades. Although it has played a role in cancer, interest in the strategy has been reawakened by deepening knowledge of drug resistance mechanisms, tumor immune surveillance, and how the tumor microenvironment determines the way that tumor cells behave and respond to cytotoxic or targeted agents. Where before, cancer drug combinations were largely a matter of trial and error, they can now be pursued on a more rational basis.

But a greater stimulant to combination therapy has been the recent emergence of checkpoint inhibitors and other immuno-therapies. Pharma has primarily pursued partnerships to access assets — immuno- oncology or targeted agents – to test with its internal immuno-oncology candidates. Some of the more notable have been Celgene Corp’s partnership with Juno Therapeutics Inc. and Pfizer Inc.’s with Merck KGAA.

The preferred route to oncology combinations has been via partnerships or short-lived clinical collaborations, less so through acquisitions. (See “In Buzz Of 2015 Pharma Dealmaking, Immuno-Oncology Is Queen Bee”—IN VIVO, September 2015.) Though few dispute the benefits of combining cancer drugs, institutions as varied as the American Society of Clinical Oncology (ASCO) and the Memorial Sloan-Kettering Cancer Center have highlighted the potential of combination therapy to accelerate the unsustainable cost of cancer treatments. Others have decried the severe toxicities that can result from combining targeted therapies or immunotherapies, the 2013 study of the combination of Bristol-Myers Squibb Co.’s Yervoy and Roche’s Zelboraf (vemurafenib and vemurafenib) being a case in point. (See “Yervoy/Zelboraf Combo Trial Fails, But Sequential Study Continues” — “The Pink Sheet” DAILY, April 4, 2013.) And sometimes combinations, for reasons of biology or trial design issues, fail to deliver the expected additive or synergistic benefits. (See “Cancer Trials & Tribulations: Combinations Are Easier Said Than Done” — Pharmaceutical Approvals Monthly, August 2014.)

TG thinks it has a better idea. Rather than partner one’s way to what CEO Michael Weiss calls “magical” combinations, TG would focus on licensing in superior oncology assets with complementary mechanisms at relatively low cost.

The vision required the ability to identify and evaluate the desired drugs. Ublituximab was easy. CD20 antibodies had been in humans for several decades, and their role in depleting B cells was well established. “We had close to perfect information,” says Weiss. The leap here lay in understanding that 1101 was a glycoengineered antibody (meaning its sugar molecules had been manipulated to improve the antibody’s ability to bind to immune effector cells) engineered with low fucose content, which binds to a unique epitope on the CD20 antigen. That made it more potent with respect to antibody-dependent cell-mediated cytotoxicity (ADCC). And understanding what the superior potency could mean for drug combinations, and for patients.

The 1303 backbone consists of superior versions of biologically validated agents, each with a history of use in humans. Ben Bonfaint, partner at consultancy Triangle Insights, points out that TG’s strategy of starting with established mechanisms, and building on that with incrementally riskier assets, avoids the potential pitfall of going before FDA with two novel mechanisms and layering the risk.

Gilead Sciences Inc., through its 2011 acquisition of Calistoga Pharmaceuticals Inc., had shown that hitting PI3K delta was a mechanism for regressing tumors. TG put 1202 through rigorous testing at Duke University in serum derived from CLL patients, and verified that it was equal in potency to
Gilead’s Zydelig (idelalisib). The preclinical testing also suggested that it would be less toxic than Zydelig, with a longer half-life that would allow QD dosing, a competitive advantage in the class.

When searching for a PI3K delta inhibitor, Weiss says that he passed over some candidates that were more potent than the one he chose. “My rule is that you need to have a threshold of low nanomolar potency but the lowest is not necessarily the best.” Potency is one part of the equation. Extensive toxicity data for 1202 persuaded him to license the drug.

The more recent licenses, to the IRAK4 inhibitor and to the checkpoints, introduced some target risk into the portfolio. These assets were also licensed at an earlier stage, the IRAK4 before toxicity data were available. But research published by Nimbus Therapeutics suggests that IRAK4 is a therapeutic target for diseases driven by aberrant oncogenic MYD88 signaling, and plays a role in B-cell lymphoma and in autoimmune diseases – TG’s sweet spot. Weiss sees a place for it as lymphoma and in autoimmune diseases – MYd88 signaling, and plays a role in B-cell for diseases driven by aberrant oncogenic suggests that IRAK4 is a therapeutic target — present obvious combo potential and don’t require overthinking. “You don’t need an advanced degree in molecular biology to think maybe we should try 1101 or 1202 with ibrutinib or with a PD-1.”

TG is a small company of about 35 employees. It relies on vendors and academia for research and manufacturing support, not so much on CROs as it considers clinical trial design and execution a core capability. Sometimes combination possibilities that aren’t so obvious come to it through its research partners. Research it commissioned at Columbia University Medical Center yielded an oral presentation at ASH 2015, the annual meeting of the American Hematology Society, describing impressive synergies in the combination of PI3K delta inhibitor TGR-1202 and Amgen Inc.’s proteasome inhibitor carfilzomib in treating aggressive lymphomas and, potentially, solid tumors. Gilead’s Zydelig and Takeda Pharmaceutical Co. Ltd.’s Velcade, which were also in the mix of possible combinations, did not demonstrate the same level of synergy.

And though TG downplays its science credentials, it relies on a few internal experts and others in its network, as well as its internal database of past combinations, to guide it in rational combos and sequencing, particularly with immuno-oncology assets. For example: TG had reported preliminary Phase I/II results from its ongoing dose escalation study of 1101 plus 1202 (TG-1303) in heavily pre-treated CLL patients. “There were almost no CLL/SLL [small lymphocytic lymphoma] patients that were not stable or better through two months,” says Weiss. The combo was safe with neutropenia being the only grade 3/4 adverse event greater than 5%.

His team concluded that there is no reason to start the PD-1 inhibitor (in the Phase I/II trial at University of Pennsylvania) at day one. Patients are getting high doses of CD20; they’re just getting up to high doses of PI3K delta; the PD-1 is not needed until the third month. “We think we’ve reduced the tumor burden in all patients by 50% to 70% by the time we start them on an agent that will engage T cells, with the potential for cytokine storm and so forth,” says Weiss. The idea is to introduce the PD-1 into a lower tumor burden environment and give it the best chance of working with the least amount of toxicity.

TG is confident that 1101 and 1202 will remain the backbone for further combinations in both cancer and autoimmune disease. IRAK4 could be an add-on in cancer, but

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**Exhibit 1**

**Summary Of TG Therapeutics Portfolio By Level Of Validation**

<table>
<thead>
<tr>
<th>ASSET</th>
<th>LICENSER, DATE</th>
<th>STAGE AT LICENSE</th>
<th>TARGET RISK</th>
<th>TOXICITY DATA</th>
<th>THERAPEUTIC AREA APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20 antibody (TG-1101)</td>
<td>LFB, March 2012</td>
<td>PI/II</td>
<td>Low</td>
<td>Yes</td>
<td>B-cell cancers, autoimmune</td>
</tr>
<tr>
<td>PI3K delta (TGR-1202)</td>
<td>Rhizen, August 2012 (Sept. 2014 exercise option for global rights)</td>
<td>Preclinical</td>
<td>Low</td>
<td>Yes</td>
<td>B-cell cancers, autoimmune</td>
</tr>
<tr>
<td>IRAK4</td>
<td>Ligand, June 2014</td>
<td>Preclinical</td>
<td>High</td>
<td>No</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>PD-L1 GITR</td>
<td>Checkpoint Therapeutics, March 2015</td>
<td>Preclinical</td>
<td>Moderate High</td>
<td>No No</td>
<td>Blood cancers</td>
</tr>
</tbody>
</table>

**SOURCES:** Strategic Transactions; TG Therapeutics; Word Control
Weiss thinks it will find its utility combined with 1303 in certain autoimmune diseases where it makes sense to add inhibition of the IL-1 pathway to the basic mechanism of B-cell depletion. same with the checkpoint assets: once they’ve cleared early-stage testing, and the anti-GiTR antibody has been validated, the likely plan will be to layer them onto 1303 in hematologic cancers. That’s another potentially “magical” combination.

AVOIDING FOREIGN ENTANGLEMENTS

The second element in TG’s business model, the avoidance of R&D partnerships, while not unique, sets up an unprecedented dynamic in tandem with TG’s proprietary combination strategy.

Weiss takes exception to the view of many investors and sell-side analysts who see marquee partnerships with big pharma as a validating event for a young biotech. He thinks that many young companies, especially those backed by VCs, do deals too early and in some cases destroy future value for shareholders. He concedes that avoiding partnerships could be negatively affecting the way the market values TG Therapeutics. But he also maintains that the smartest investors recognize that deals can be dilutive and not confirming of value.

Weiss thinks the biotech industry is in a cycle where there is a naïve and transient investor base not always up to making its own assessments. In fact, he believes that tapping Wall Street is invariably less dilutive than doing a big partnership early on. He feels fortunate in having strong investors behind him who can fund the company at reasonable valuations. TG currently has about $115 million in cash and equivalents and little debt. It prefers to raise capital through periodic small financings.

But Weiss’ aversion to R&D partnerships and premature commercial deals goes beyond the financial dimension. He believes they are a headache to negotiate and manage, and can often, especially when partnering over a combination regimen, lead to sub-optimal trial protocols. At a recent earnings call, talking about TG’s resistance to partnerships in the cancer business, Weiss said, “We see it as a complicated matrix of what we’re interested in achieving in terms of these combinations, and trying to identify a partner that may share our long-term vision just did not make it interesting for us to explore opportunities on that side.”

Cancer is TG’s core business; autoimmune is a complementary revenue stream. TG has the cash and it has the confidence to go it alone with respect to the cancer business. Because of the higher cost of building an autoimmune franchise, Weiss will be more welcoming to big pharma partners at an earlier stage.

In the US, Weiss is comfortable with building out a cancer sales force as TG approaches the market. He’ll make a decision about whether to do so in Europe, or to take a partner; but he’s fine with setting up a commercial organization in Europe if need be. Japan, ROW – he’s open to any kind of partnership that makes sense.

While not keen on partnering, Weiss and his team have been busy on the licensing front, bringing in quality assets for relatively low up-fronts consisting of cash or equity, and modest downstream payments.

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* No instances of colitis observed.


SOURCE: TGTX ASCO 2015 Analyst and Investor Event
ITS THE SAFETY, STUPID!

Although 1101 and 1202 have proven to be as potent or more so than drugs of the same class, TG is counting on their safety profile to differentiate them in the CLL and non-Hodgkin’s lymphoma (NHL) landscape. Not only will they be easier on cancer patients, the company hopes that they’ll allow patients – particularly older, frailer ones – to continue longer on treatment. And they’ll be more combinable with other drugs.

Weiss is confident that superior safety will influence payers, particularly when toxicity ends up costing them in hospitalization and expensive interventions. He recognizes that in the most lethal cancers, particularly when efficacy is especially strong, or in second- and third-line settings, that safety can sometimes take a back seat. But he’s counting on oncologists and patients to demand TG’s regimens.

He points out that a lot of PhDs have recently come into the industry. “The industry was more diverse 10 years ago,” he says, “with more MDs and people with good scientific backgrounds but also good common sense.” Scientists tend to be focused on efficacy. They deal with rats and Petrie dishes, and are typically not used to interacting with patients. Weiss speculates that this might make some scientist-executives and even investors less sensitive to risk/benefit considerations that physicians and patients care about.

The safety profile of 1202, TG’s PI3K delta inhibitor, especially with respect to discontinuations from hepatic toxicity and colitis, is particularly striking compared with its peers, AbbVie Inc.’s duvelisib and Gilead’s idelalisib. (See Exhibit 2.)

In January 2013, TG initiated a single-agent dose escalation trial of 1202 in patients with relapsed/refractory hematologic tumors. Preliminary data from this study were presented at the June 2015 ASCO meeting. Grade 3/4 adverse events in 66 patients were highest for neutropenia (11%) and anemia (8%); all other AEs were 0% or single digits less than or equal to 5%.

TG updated these data in a poster at ASH 2015: in 75 subjects with a variety of relapsed/refractory B-cell malignancies, no grade 3 or greater adverse events were seen in more than 10% of patients. “Incidence of hepatic toxicity and colitis appear significantly less than that reported with other agents in this class,” said Owen O’Connor MD, PhD, of Columbia University Medical Center.

KICKING THE TIRES ON TG’S MODEL

The test of a new business model is (1) whether it presents a new way to generate returns, and (2) whether it attracts imitators. It’s too early to answer the first question, and
the answer to the second is a decisive Yes.

It should be noted that there have been biotech companies in the past that have incorporated at least one of the elements of TG’s model, albeit with significant differences. Ben Bonifant cites Celator Pharmaceuticals Inc., a 13-year-old biotech based on developing synergistic ratios of chemotherapeutic drugs delivered in a proprietary nanoscale vehicle. The company’s lead product, a combination regimen for acute myeloid leukemia (AML), is in a pivotal trial.

TG isn’t interested in pursuing a wide variety of tumors, and it’s been cautious in its use of cytotoxic drugs in its combinations. It is more focused on matching complementary mechanisms. Concentrating on a specific class of cancers has allowed it to develop a backbone regimen that works across B-cell malignancies (and potentially autoimmune diseases) yet is benign enough to permit further add-ons. Also, unlike TG, Celator is open to partnerships, research collaborations and out-licensing deals.

Gilead is renowned for developing best-in-class proprietary combinations for HCV and HIV. Moreover, the company’s combination regimens work across the subtypes in each indication, especially HCV, and in that way are similar to TG’s combinations. However, Gilead has not internalized combination therapy to the extent that TG has; it does not appear to be, for instance, a committed feature of its inflammatory or cardiovascular franchises. Also, Gilead has shown itself quite open to R&D alliances, particularly discovery collaborations.

TG was founded on a vision of wholly owned combinations – doublet, triplet and quad – for serious cancers. It found that the best way to pursue that vision was on its own without a pharma partner. And it has taken a novel approach to how it calibrates the balance in its drugs between efficacy and safety. No single element in its model is unprecedented. But working together, particularly in the age of combination treatments, they enable and reinforce one another in a unique way.

The model is certainly vulnerable to imitators. At a Merrill Lynch conference in September 2015, Incyte Corp. emphasized its growing stable of proprietary assets – PD-1, PD-L1, IDO1, FGFR and BRD inhibitors, PI3K delta and JAK1, and preclinical candidates GfTR, OX40, TIM-3 and LAG-3. Chief Scientific Officer Reid Huber, PhD, spoke of the company’s intention to test novel combinations of its drugs. Of course, Incyte’s therapeutic focus will be considerably broader than TG’s, ranging over the hematologic and solid tumor landscape.

But TG is also exposed to direct competition to its specific drug combinations and the indications they target. The combo of Gilead’s Zydelig plus rituximab has been approved in the US for relapsed CLL patients; it has shown the following adverse events greater than or equal to grade 3: neutropenia (37%), increased lymphocyte count (18%) and lymphopenia (9%). Serious adverse events occurred in 49% of patients: pneumonia (17%), pyrexia (9%) and sepsis (8%).

Weiss sees the triplets of Zydelig plus bendamustine plus Rituxan and of Imbruvica plus bendamustine plus Rituxan in advanced CLL – both have reported Phase III results – as the primary competition for Imbruvica plus TG-1101 in relapsed/refractory patients, especially in the community setting. He adds, “TG-1303 will compete in both frontline and relapsed/refractory settings.”

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Note: 3 patients (~5%) have come off study due to an adverse event, none related to hepatic toxicity or colitis.

SOURCE: TGTX presentation at ICML conference, June 2015
Zydelig alone is quite toxic and carries a black box warning for “fatal and serious toxicities” including hepatic, colitis, pneumonitis and intestinal perforation.

The safety profile of TG-1303, from a June 2015 presentation of data from its ongoing Phase I/I trial in 55 heavily pretreated patients appears in Exhibit 3.

Bonifant says that TG-1303, should it reach the market, is open to fast followers with an already approved component; all they need do is quickly demonstrate the efficacy of their product with another approved product. Or with one of TG’s components. And oncologists have the option of putting together a similar combination with components they select.

TG’s protection – IP covering its novel combinations is not available to it – is the superior safety of its combinations. That, and the significant head start it has with two Phase III trials running and a registration trial of 1303 in NHL patients on deck, allowing it the time to test add-on improvements to 1303. Its checkpoints, for instance, will likely enter the clinic in 2016, making TG the first company to bring a proprietary triplet including 1303 plus a PD-L1 into the clinic. In fact, the triplet Phase I trial of 1303 plus pembrolizumab at the University of Pennsylvania will provide an early read on combining 1303 with a checkpoint inhibitor. So as long as TG stays adept, continues to keep ahead of the pack by initiating new trials and by licensing in complementary assets that are safe and potent, the model stands a good chance of holding up.

For now, Weiss is not emphasizing solid tumors; in fact, the deal with Checkpoint Therapeutics stipulates that TG can apply the assets to hematologic cancers, while Checkpoint Therapeutics reserves their use in solid tumors. However, the company is already exploring the utility of PI3K in solid tumors in a Phase I trial of 1202 as single agent or in combination with nab-paclitaxel/gemcitabine or with FOLFOX.

TG’s next act – building an autoimmune disease franchise – is already in motion. As management disclosed in its third-quarter 2015 earnings call, it will follow the lead of Roche, which recently showed impressive results in late-stage trials of its CD20 antibody ocrelizumab in both primary progressive and relapsing forms of multiple sclerosis. TG will do a Phase I/I trial in 2016 and will likely initiate a Phase III trial in 1H17. One sequencing option it’s considering is starting patients on IV CD20 and continuing them on oral PI3K therapy, maybe adding an oral IRAK4 inhibitor to the mix.

As for the long game, Weiss is open to the company being acquired. He’s not interested in a dismantling acquisition, where a suitor is drawn just by the PI3K drug or the CD20 in autoimmune disease, and carves those out and shuts down the company. But he would consider an attractive offer by an acquirer who “believed in what we’re doing” and could accelerate it and create a faster, bigger platform. “We would work within that structure, and hopefully be able to continue to do what we’re trying to accomplish.”

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Navigating Patent Minefields In Emerging Asian Medtech Markets

Success in the Emerging Asian Markets (EAMs) requires medical device companies to ensure superior product and patent protection for both their products and related methods of use, given the ease with which devices can be copied by competitors.

BY GABRIELA COMAN

In China, India, Indonesia, Korea, Malaysia, the Philippines, Taiwan, Thailand, Mongolia, Pakistan, Sri Lanka and Vietnam – the countries that can be grouped together as the Emerging Asian Markets (EAMs) – securing patent protection is critical. Once in possession of a patent, a medical device company will be able to create legal barriers to entry for competing devices by preventing others from copying, selling or manufacturing the patented device. It will also be able to license the patented device to generate revenues.

Furthermore, the value of the medical device company can be enhanced via the equity and asset building associated with the patent, which in turn may attract further investment.

Five Factors to Forestall Failure

But early in the pathway leading to an EAM launch of a medical device, there are five factors that a company needs to consider or act on, centering around:

- **Core Technology Assessments And Tailoring Patent Portfolios To Individual EAMs**
  Medical device companies interested in not-fully-developed patent markets, such as the EAMs, should develop a product patent portfolio that is tailored to the needs of each respective emerging market. The first stage for the medical device company is to assess the core technology and file patent applications that are designed to provide the broadest possible coverage of the core technology.
  The company must consider: its current and future business development objectives; the ways that local competitors could design around its patented devices; the specific needs of the markets targeted – the Chinese vascular or ultrasound scan market or the Indian orthopedic market, say – and the way the patented technology could affect them; and whether to file national, regional or PCT (patent cooperation treaty) applications.
  Broad patent coverage, when and where applicable, should be

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EAM patents applicants need to be aware of current and future business development objectives, market specifics and how local competitors could design around the patented devices of the company.

Filing in multiple countries can be prohibitively expensive, but mechanisms to control fees and costs include international application/PCT applications, or concepts such as the newly launched ASEAN Patent Examination Cooperation program.

All EAM countries observe a “first-to-file” rule in granting patents, which, in cases where two different entities apply for a patent, it is the first one to file an application that will obtain the patent if the invention is patentable. The US adopted this law in 2013.

What is patentable and what is not can be something of a minefield, with different EAMs applying different criteria to patentable matter, so the regulations of each country require careful scrutiny.

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directed to the entire medical device, its components, methods of manufacturing, methods of use and treatment, therapeutic uses and any other aspects of the invention. For example, for sophisticated medical devices like blood glucose monitoring systems, claims directed to user interface, software, power-management system and IC chips, among others, may also be filed separately to protect fully the scope of the claimed invention.

Patentable Matter May Be Different In The EAMs Compared With The US/Europe

Medical devices are protected and patentable in EAM countries and the US. Methods of surgery and medical treatment methods may be protected and patentable in the US and Australia, but they are typically not protected in Europe or in EAM countries such as China, India or Thailand.

In most countries, methods that include a surgical step on a human or animal body are not patentable, even if the effect of surgery is not therapeutic. Claim terms such as “non-medical” or “diagnostic” could be used to make a claim acceptable (provided that the claim could be reasonably interpreted to be directed to a non-medical method without producing a therapeutic effect).

CHINA

In China, neither methods of medical treatment nor diagnostic methods are patentable subject matter. However, devices and apparatus for implementing these methods of diagnosis or medical treatment, including substances and compositions for use in such methods, are patentable subject matter. For claims of treatment of diseases, these could be written in the form of pharmaceutical or use claims such as “method for preparing a pharmaceutical.” Also, the scope of the claims must be commensurate with the working examples provided in the specification.

INDIA

Similarly, in India, methods of surgical treatment of the human or animal body (by surgery or therapy) or methods of diagnosis are not patentable subject matter.

Patents may be obtainable, however, for surgical, therapeutic or diagnostic instruments or apparatus. In addition, the manufacture of prostheses or artificial limbs, and taking measurements of the human body, may be patentable.

KOREA/THAILAND

In Korea, methods of treating humans are not patentable. However, methods of treating non-human animals are patentable, as are methods which are non-therapeutic, such as cosmetic applications. In Thailand, methods of medical treatment are not patentable subject matter.

In contrast, in the US, surgical techniques and methods of medical treatment, as well as methods of diagnosis or treatment, are patentable subject matter. For example, an instrument that cuts bone in a retrograde manner to form a bone tunnel or socket may be patentable in both the US and in the EAMs. A method of arthroscopic surgery to form a bone tunnel or socket using a retrograde cut-off instrument may be patentable in the US but not in most EAM countries, where methods of medical treatment are unpatentable.

Patent Standards And Systems Are Different In EAM Countries

EAM countries apply various patent standards when assessing whether a medical device invention is patentable. These standards are different from those applied in the US, that is, novelty and non-obviousness. Under Chapter 35 of the USC (United States Code) in §§102, 103, it states that an invention must be novel and non-obvious to be patentable.

The requirement of novelty means that the invention (medical device or method) must be new, that is, not previously known or used by others. The requirement of non-obviousness means that the invention must not be an obvious variation or combination of subject matter previously known to those of ordinary skill in the art.

In India, the patentability requirements for an invention are: novelty (the medical device must be new), non-obviousness (the medical device has to involve an inventive step), and industrial applicability (the medical device can be made or used in industry). Apart from satisfying these criteria, the invention should also not fall under the category of non-patentable subject matter of the Indian Patent Act.

China adopts a dual approach in determining whether an invention could be considered inventive and thus patentable: “prominent substantive features” and “notable progress.” Article 22 (3) of the Patent Law of the People’s Republic of China prescribes that “inventiveness means that, as compared with the technology existing before the date of filing, the invention has prominent substantive features and represents notable progress, and that the utility model has substantive features and represents progress.” Under China’s Guidelines on Examination of Patents, “prominent substantive features” refer to “non-obviousness” and the examiner must conduct tests to establish the proximate prior art and the distinctive features of the invention and the technology issue to be solved, and must make a judgment on whether the invention seeking to be protected has obviousness to those skilled in the art.

“Notable progress” may be shown in the form of the “effect” of the invention or the “useful technological effective result.” The Guidelines on Examination of Patents interpret the useful “effect” as: an invention that has a better effect than the prior art, an invention that has a technical solution involving a totally different concept but that has a similar effective result to the prior art, and an invention that represents a new trend of technological development.

In Korea, the criterion applied is whether it would be difficult for a person skilled in the art to arrive at the claimed invention.

All EAM countries observe a “first-to-file” rule in granting patents, a rule that was adopted in the US in 2013. Under “first to file,” when two different entities apply for a patent, the first one to file an application will obtain the patent if the invention is patentable. The US move to a “first-to-file” rule was a change from its prior “first-to-invent” rule. US patent law adopted this major change to harmonize its patent process with that of the European Patent Office (EPO) and those of other foreign countries. In an effort to ease the transition from the “first-to-invent” to the “first-to-file” system, US patent law provides a one-year grace period, meaning that the inventor (or the person who directly obtained the information from the inventor) has the right to publish his/her invention within a year of filing the application without losing patent rights.
In contrast, no EAM countries observe a grace period. Most countries of the EAM group – and in Europe – apply an absolute novelty standard, meaning that any public disclosure of invention before the filing of a patent application will render the invention unpatentable. If the invention has become publicly available in any way prior to the filing of the application, the application will be rejected. “Publicly available” is typically defined as including: selling the invention; publishing the invention in a printed publication, such as a specialist brochure or magazine; giving a lecture about the invention; or presenting it to an investor without a non-disclosure agreement. The invention may be made “publicly available” by anyone, including the inventor(s) or any independent third party. Thus, if an inventor releases – before the filing of a patent application – a surgical brochure describing a medical device, the inventor will be barred from obtaining patent protection for the medical device in the EAM countries, whereas in the US, the inventor has one year from the release of the surgical brochure to file a patent application.

Best mode requirement is not a prerequisite to patentability in Taiwan and Korea. In Thailand and India, the patent specification must include the best method for performing the invention known to the applicant. In China, the specification must sufficiently describe details about the “preferred embodiments” or “optimized embodiments” but no oath from the applicant is required.

Opposition proceedings are not available in Taiwan (but relevant prior art may be submitted for consideration) and China (but patent invalidation may be available after grant of the patent). India, Thailand and Korea provide opposition proceedings. India, for example, allows for pre-grant opposition any time before publication and post-grant before expiration of a one-year period from the publication of the grant of the patent.

Filing Costs Are Different For National, Regional And PCT Applications

A patent is only enforceable in the jurisdiction in which it is granted. If a medical device company seeks worldwide protection of a medical device, it must file a patent in each individual country worldwide. Filing in multiple countries, however, can be prohibitively expensive.

All EAM countries observe a “first-to-file” rule in granting patents, a rule that was adopted in the US in 2013. Under “first to file,” when two different entities apply for a patent, the first one to file an application will obtain the patent if the invention is patentable. The US move to a “first-to-file” rule was a change from its prior “first-to-invent” rule.

Various fees are associated with securing a patent. These fees include filing fees, fees for prosecuting the application, issue and maintenance fees, once the application has matured into a patent, and attorney fees, among others. Depending on the country or region, these fees may vary widely and may be spread unevenly over the course of filing and prosecuting an application, and maintenance of the patent.

One method of controlling these costs is the filing of an international application or a PCT application. The international application does not mature into a single international patent; however, it provides the company with the opportunity to delay making a final decision on whether to file a national application in member countries – for up to 30 months in most countries. During this period of time, the company applying for the patent can: assess whether the medical device is commercially viable, raise funds, explore potential markets and decide whether to enter the national/regional phase.

For the over 100 countries that are not members of the PCT (including Asian countries such as Cambodia and Myanmar), a patent application must be filed with the national patent office of the specific country to secure patent protection in that country. Direct national filing avoids the costs associated with the intermediate steps of filing via the PCT or a regional patent office prior to filing nationally.

ASEAN (the Association of Southeast Asian Nations) Patent Examination Cooperation (also known as ASPEC) has been recently launched as a regional patent cooperation program for sharing patent searches and examination results. ASPEC resembles a regional network of patent prosecution highways (PPHs) in the sense that each of the nine IP offices in the ASEAN countries accepts a patent application for expedited examination and search. In this manner, the results of search and examination from one country are used to expedite progress in the other countries.

Enforcement Of Patent Rights In EAM Countries May Be Limited

As noted, what may be patentable in the US may not be patentable in EAM countries and, even if patented, enforcement of the patented subject matter varies greatly. For example, methods of medical treatment are considered to fall outside the scope of patent protection in most countries including South Korea and European countries.

Although EAM countries have been gradually revising their patent laws to render patents more valuable, medical device companies are not well-positioned when it comes to patent litigation and enforcing patent rights.

For example, while the courts in India (the District Court or a High Court) have gradually changed their understanding of complex patent infringement and validity issues, India still ranked as last in the Global Intellectual Property Center Index of 2014 (conducted by the US Chamber of Commerce), due mainly to its weak IP protection and enforcement.
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<th>HENN, Timothy</th>
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<td>To: Cardiac Dimensions Inc., Pres. &amp; CEO (December)</td>
<td>To: CardioDx Inc., CFO (December)</td>
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<tr>
<td>From: AccessClosure Inc., Pres. &amp; CEO</td>
<td>From: Crescendo Biosciences Inc., CFO</td>
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<tr>
<td>Phone: 425-605-5900</td>
<td>Phone: 650-475-2788</td>
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<th>COLLARD, Craig A.</th>
<th>HOLDENER, Ed</th>
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<td>To: Veloxis Pharmaceuticals AS, Pres. &amp; CEO (December)</td>
<td>To: Novimmune SA, Chmn. &amp; CEO (December)</td>
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<tr>
<td>From: Cornerstone Therapeutics Inc., Chmn. &amp; CEO</td>
<td>From: Roche, CMO</td>
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<tr>
<td>Phone: +45 70 33 33 00</td>
<td>Phone: +41 22 839 71 41</td>
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<th>CREECH, Timothy</th>
<th>HOROBIN, Joanna</th>
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<td>To: Heat Biologics Inc., CFO (December)</td>
<td>To: Idera Pharmaceuticals Inc., SVP, CMO (November)</td>
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<tr>
<td>From: Salix Pharmaceuticals Inc., Acting CFO</td>
<td>From: Verastem Inc., CMO</td>
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<tr>
<td>Phone: 919-240-7133</td>
<td>Phone: 617-679-5500</td>
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<th>KANTAK, Seema, PhD</th>
<th>LABINGER, Barry</th>
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<tr>
<td>To: Symic Biomedical Inc., CSO (December)</td>
<td>To: Biothera Pharmaceutical Inc., CEO (December)</td>
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<tr>
<td>Phone: 415-805-9005</td>
<td>Phone: 651-675-0300</td>
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<tr>
<th>KATZER, Charles</th>
<th>LAPPALAINEN, Jaakko, MD, PhD</th>
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<tr>
<td>To: Innocoll AG, Head, Mfg. &amp; Tech. Ops. (December)</td>
<td>To: Marinus Pharmaceuticals Inc., VP, Clinical Dev. (December)</td>
</tr>
<tr>
<td>Phone: +353 90 648 6834</td>
<td>Phone: 484-801-4670</td>
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<th>LIU, Hui, PhD</th>
<th>MARKWOOD, Jeffrey</th>
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<td>To: Merus BV, CBO (December)</td>
<td>To: Signostics Ltd., CFO (December)</td>
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<tr>
<td>From: Novartis Oncology, Global Head, Bus. Dev. &amp; Licensing</td>
<td>From: SonoSite Inc., Senior Dir., Corp. Planning &amp; Finance</td>
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| MCCALLUM, Stewart, MD | |
|---------------------| |
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| From: GlaxoSmithKline PLC, Clin. Dir., Academic & Sirtuin, Discovery Performance | |
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MCCARTHY, William
To: Ignyta Inc., CBO (December)
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MILLER, Lisa A.
To: Metabolon Inc., VP, General Mgr., Precision Medicine (December)
From: Prometheus Laboratories Inc., Pres. & CEO
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MILLER, Neil, PhD
To: Auspherix Ltd., CSO (December)
From: GlaxoSmithKline PLC, Senior Dir, Head, Chemistry DMPK & External Discovery, Singapore
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To: Therapeutic Proteins International LLC, CEO (November)
From: Bristol-Myers Squibb Co., VP Biologics Dev. & Ops.
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MOHS, Richard, PhD
To: AgeneBio Inc., VP, Clinical Dev. (December)
From: Eli Lilly Research Laboratories, VP, Neuroscience Early Childhood Dev.
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MOWEN, Kerri, PhD
To: Padlock Therapeutics, Dir, Biology (January)
From: The Scripps Research Institute, Associate Professor
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PADMANABHAN, Raj
To: Paratek Pharmaceuticals Inc., VP, Information Technology (December)
From: Cubist Pharmaceuticals Inc., Senior Dir, IT Architecture, Quality & Processes
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SKWIERCZYNSKI, Raymond D., PhD
To: CoLucid Pharmaceuticals Inc., Head, Pharmaceutical Ops. (December)
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To: Minnetronix Inc., VP, Engineering & Technology (November)
From: Hansen Medical Inc., COO
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To: Kite Pharma Inc., Chief Commercial Officer (December)
From: Pharmacyclics Inc., Chief Commercial Officer
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TWYMAN, Mark
To: Novavax Inc., VP, Mktg. (December)
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VAN DER GRAFF, Piet, PharmD
To: Certara, VP, Quantitative Systems Pharmacology (December)
From: Leiden Academic Center for Drug Research, Dir.
Phone: 609-716-7900

VICKERS, Steven
To: Chiasma Inc., VP, Sales (January)
From: Onyx Pharmaceuticals Inc., Senior National Sales Dir, Hematology
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WILSON, Alain
To: Antibe Therapeutics Inc., CFO (December)
From: Management Consultant
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To: Bind Therapeutics Inc., CSO (December)
From: Bristol-Myers Squibb Co., VP, Oncology Discovery & Translational Research
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BONNEY, Michael
To: Alnylam Pharmaceuticals Inc., Chairman (January)
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BUTLER, John P.
To: Keryx Biopharmaceuticals Inc., Director (December)
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To: Acerus Pharmaceuticals Corp., Director (December)
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To: St. Jude Medical Inc.
New Title: Pres. & CEO (January)
Previous Title: COO
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SUNDSTROM, Lisa
To: Sanuwave Health Inc.
New Title: CFO (December)
Previous Title: Interim CFO
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TILES, Ron
To: Turing Pharmaceuticals AG
New Title: Chmn. & Interim CEO (December)
Previous Title: Chmn.
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VAN DEN BOOM, Dirk
To: Sequenom Inc.
New Title: Pres. & CEO (December)
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WHITE, Ted
To: Aqua Pharmaceuticals LLC
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WILSON, Angela
To: NantKwest Inc.
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Marking The 20th Anniversary Of The European Medicines Agency

We commemorate the 20th anniversary with this special report that discusses the EMA’s achievements, its shortcomings, and the future of EMA and EU pharmaceutical regulation.

www.PharmaMedtechBI.com/EMA20th
This issue’s Dealmaking covers deals made:

December 2015

Derived from Strategic Transactions, Informa’s premium source for tracking life sciences deal activity, the Dealmaking column is a survey of recent health care transactions listed by relevant industry segment – In Vitro Diagnostics, Medical Devices, Pharmaceuticals, and Research, Analytical Equipment and Supplies – and then categorized by type – Acquisition, Alliance, or Financing.

**IN VITRO DIAGNOSTICS**

**Alliances**

AEterna Zentaris gets some US rights to Armune’s Apifiyn prostate cancer test

**Financings**

Nanosphere nets $9.1mm via RDO

T2 Biosystems nets $32mm through public offering

**MEDICAL DEVICES**

**Mergers & Acquisitions**

CooperSurgical buys Research Instruments for $51mm

CryoLife pays $130mm in cash and stock for heart valve maker On-X Life Technologies

Getinge acquires Stericool for undisclosed sum

Medical Developments buys Avita’s respiratory business

**Alliances**

Acelity acquires the SNaP negative wound pressure therapy system from Spiracur

BSN Medical, Ortopedicos Futuro form JVs in Columbia and Ecuador

GSK signs medication adherence collaboration with Propeller Health

Medtronic, Samsung ally again, this time in neuro

Toshiba America Medical, Ziehm Imaging to offer imaging solutions to US customers

**Financings**

CryoLife secures credit facility to fund acquisition of On-X Life

HART enters into $15mm common stock purchase agreement

NeuroMetrix raises $13.8mm in preferred stock private placement

SeaSpine enters $30mm credit facility agreement with Wells Fargo

**PHARMACEUTICALS**

**Mergers & Acquisitions**

AstraZeneca pays $2.5bn, plus earn-outs, for majority stake in Acerta Pharma

AstraZeneca buys Takeda’s respiratory business for $575mm

Sanofi and Boehringer enter discussions to swap key businesses; Boehringer would pay €4.7bn cash

Cytos, Kuros merge to form leader in tissue repair and orthobiologics

Horizon Pharma acquires Crelata for $510mm

SK Capital buys IBA Molecular from CapVest

Ligand buys antibody discovery firm OMT for $178mm

**Alliances**

Mitsubishi Tanabe gets rights to Akebia’s vadadustat for CKD-related anemia

Amgen, Merck ally in combination trials

Arsia, Biogen partner in subcutaneous hemophilia therapies

Aegensys, Bellicum ally in CART therapies

Biovista pens COSS deal with Astellas

EUSA Pharma gets exclusive tivozanib rights from Aveo in Europe and other select countries

Bavarian Nordic, Janssen ally in HPV vaccines

Bayer, CRISPR form gene editing JV to cure blood disorders, blindness, and congenital heart disease

Innovus chooses Bio Task to sell its products in Malaysia

BioAtta, Pfizer partner in cancer antibody therapies

Viiv acquires Bristol’s early- and late-stage HIV candidates

NeoN, Bristol test NEOPV01/Opdivo combination

Chong Kun Dang to sell Cardiome’s Brinavess in South Korea

Celgene, Inception IBD form collaboration involving ulcerative colitis and Crohn’s

Chong Kun to sell Neovacs’ IFN-alpha kinase vaccine in South Korea

CKD gets rights to sell S1’s Lorexys in South Korea

Takeda partners with Cour for celiac disease immune therapy

XL-protein applies technology to Easton targets

Gilead gets filgotinib rights from Galapagos; deal value could top $2bn

Galena sells Zuplenz US rights to Midatech

Zymeworks and GSK enter into collaboration for antibodies

Lilly is Halozyme’s latest Enhance partner

Intrexon partners ActoBiotics platform with Janssen in metabolic disorders

Ligand licenses three Captisol-enabled programs to Rodes

Mallinckrodt buys three of The Medicine’s Co.’s hemostasis products for $175mm plus milestones

Xoma partners XMetA antibody program with Novo Nordisk

Roche teams with Pieris in immuno-oncology

Roche signs autologous cell therapy deal with SQZ

Boehringer and MD Anderson collaborate in pancreatic cancer

Proximagen partners VAP-1 inhibitor with Roche

**Financings**

Aeolus raises $6.7mm in PIPE

AEterna Zentaris nets $15.4mm through public offering

AntriBio gets initial $2mm of possible $15mm private placement

BioPharmX raises $5.9mm in PIPE
IN VITRO DIAGNOSTICS

Alliances
/In Vitro Diagnostics

AETerna Zentaris Inc., ARMUNE Bioscience Inc.

Armune BioScience Inc. granted Aeterna Zentaris Inc. rights to sell its Apifiny prostate cancer diagnostic to designated medical professionals in the US. For those tests that it markets, Aeterna gets sales commissions. (Dec.) Apifiny is the only cancer-specific non-PSA blood test for prostate cancer. It tests for autoantibodies produced by the immune system in response to cancer, providing physicians with an avenue for earlier detection and treatment planning. Aeterna is looking forward to promoting Apifiny as an way to get its sales force trained and exposed to the oncology market ahead of FDA approval for the company’s Phase II prostate cancer compound Zoptrex (zoptarelmin). The company also sees an opportunity for Apifiny to qualify as a companion diagnostic for Zoptrex.

Financings
/In Vitro Diagnostics

Nanosphere Inc.

Molecular diagnostics firm Nanosphere Inc. netted $9.1mm through the registered direct offering of 21.3mm common shares at $0.47 each (a 43% discount) to accredited investors. The company also issued five-year warrants to buy another 21.3mm shares exercisable at $0.70 each. Rodman & Renshaw (a unit of HC Wainwright & Co.) was the placement agent. (Dec.) Investment Banks/Advisors: HC Wainwright & Co.; Joseph Gunnar & Co.; LifeSci Capital LLC; Rodman & Renshaw Capital Group Inc.

T2 Biosystems Inc.

T2 Biosystems Inc. netted $32mm through the public sale of 3.5mm shares at $9.75. The company is developing in vitro diagnostics for hemostasis and infectious diseases utilizing its T2 Magnetic Resonance platform (T2MR). (Dec.) Investment Banks/Advisors: Canaccord Genuity Inc.; Cantor Fitzgerald & Co.; Goldman Sachs & Co.; Leerink Partners LLC.

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

Mergers & Acquisitions

ADDvise signs letter of intent to acquire LabRum for deal valued at up to $5.3mm

Honeywell acquires research chemicals business from Sigma-Aldrich

MEDICAL DEVICES

Mergers & Acquisitions
/Medical Devices

Cooper Cos. Inc., CooperSurgical Inc., Research Instruments Ltd.

CooperSurgical Inc., the women’s health device division of Cooper Cos. Inc., acquired Research Instruments Ltd. (RI), a privately held UK-based firm specializing in systems and devices for the in vitro fertilization and assisted reproductive technologies (ART) markets. The deal is valued at $51mm, or three times RI’s trailing 12-month revenues of $17:mm. (Dec.) The deal significantly enhances CooperSurgical’s own IVF offerings. RI’s micromanipulation products include the RI Witness ART management system, which uses radiofrequency identification to track and record patient sample data. The company also provides consumables (pipettes, handling systems, sedimentation chambers); lab thermometers and pH monitors; products for intracytoplasmic morphologically selected sperm injection; tools for PGD (preimplantation genetics diagnosis) biopsy; and laser-assisted hatching.

Cryolife Inc., On-X Life Technologies Inc.

In a move that gives it access to the $220mm mechanical heart valve market, Cryolife Inc., is paying $139mm – $91mm in cash and $39mm in stock (3.7mm shares) – to acquire closely held On-X Life Technologies Inc. (Dec.) To finance the acquisition, Cryolife received a commitment from Capital One, Fifth Third Bank, and Citizens Bank for a five-year senior secured facility, consisting of a $75mm term loan and a $20mm revolving credit facility. On-X is a leading provider of artificial heart valve replacement and repair products. The On-X aortic heart valve is the only mechanical valve that is FDA approved and clinically proven to be safer with less anticoagulation. The product is comprised of pure pyrolytic carbon (as opposed to silicon carbide), making it the longest lasting heart valve replacement on the market. The On-X aortic and mitral prosthetic valves have been safely implanted in about 200k patients throughout the world. On-X is also developing the Chord-X mitral chord repair device. In 2014, the company generated $33mm in revenue. Cryolife will sell the devices with On-X’s existing sales team and its own US cardiac surgery sales force. On-X’s mechanical heart valve business is complementary to Cryolife’s existing tissue valve business. Investment Banks/Advisors: Canaccord Genuity Inc. (Cryolife Inc.); Piper Jaffray & Co. (On-X Life Technologies Inc.)

Getinge AB

Getinge AB’s Infection Control business acquired Stericool, a seven-year-old private firm developing low-temperature sterilization systems. (Dec.) Stericool’s products incorporate hydrogen peroxide cold plasma technology, which provides the highest sterilization efficacy without any toxic byproducts and prevents any damage to medical equipment. The use of low-temperature sterilization is an ideal alternative for the minimally invasive surgery market because surgical devices are extremely sensitive.
to the high temperatures and pressure of steam sterilization. For 2015, Stericool’s sales are expected to hit $2.3mm. Just recently, the Infection Control business licensed exclusive worldwide distribution rights to TS03 Inc.’s Sterizone low-temperature sterilization system.

MEDICAL DEVELOPMENTS INTERNATIONAL LTD. AVITA MEDICAL LTD. Medical Developments International Ltd. (MDI) is paying $2.64mm – $2.2mm cash and either 125k MDI shares escrowed for six months or $440k cash – for Avita Medical Ltd.’s respiratory device business. (Dec.)

MDI gains Avita’s Funhaler easy-to-use small volume spacer for pediatric asthma, and Breath-A-Tech inhaler for pediatric and adult asthma and COPD. Both are sold throughout Australia. The use of spacers with a puffer delivers more medication directly into the lungs, thus making medicine more effective and reducing side effects. MDI’s respiratory portfolio includes spaces chambers which fit all asthma and COPD medication devices, plus masks and peak-flow meters for asthma management. Avita chose to divest the respiratory assets to focus on its regenerative medicine/wound care business.

Alliances /Medical Devices ACELITY LP INC. SPIRACUR INC. Acelity LP Inc. enhanced its advanced wound therapy offerings through the purchase of Spiracur Inc.’s SNaP disposable negative pressure wound therapy (NPWT) system. (Dec.)

SNaP is indicated for use in the post-acute setting, providing patients a discrete, non-powered device to treat hard-to-heal wounds. The system consists of small canister that both stores fluids (exudate) removed from the wound and generates negative pressure or suction, and also includes a hydrocolloid dressing applied over an interface layer to form a flexible seal around the wound. Acelity adds SNaP to its NPWT products sold by the company’s Kinetic Concepts Inc. (KCI) division, including the IAC Line and SensoTRAC technology.

BSN MEDICAL GMBH ORTOPEDICOS FUTURO Ortopedicos Futuro Columbia SAS Ortopedicos Futuro SA BSN Medical GMBH and Ortopedicos Futuro created a joint venture to sell compression garments in Columbia, Ecuador, and neighboring markets. (Dec.) BSN will contribute products from its vascular care portfolio, which includes the JB0ST line of compression garments and bandages for various venous and lymphatic diseases and conditions such as varicose veins, deep vein thrombosis, chronic venous insufficiency, venous ulcers, peripheral edema, and lymphedema. Ortopedicos Futuro is providing its No-Vaxx compression garments and customer access through its 23 stores throughout Columbia and Ecuador. In Columbia, the JV will operate as Ortopedicos Futuro Columbia SAS and in Ecuador as Ortopedicos Futuro SA, they will include Ortopedicos Futuro’s current operations in both countries. Through the agreement, BSN will have access to Ortopedicos Futuro’s distribution network and be the exclusive promotion partner for the No-Vaxx products. In the last six months, BSN has acquired three firms focused on the compression garment market – Wright Therapy Products, Farrow-Wrap, and JoviPak.

GLAXOSMITHKLINE PLC PROPELLER HEALTH Propeller Health agreed to nonexclusively develop and manufacture for GlaxoSmithKline PLC a custom sensor for GSK’s Ellipta dry powder inhaler to be used in asthma and COPD studies. (Dec.)

GSK has the option to negotiate exclusive commercialization rights to the sensor for its marketed respiratory drugs administered by Ellipta. Propeller already has a partnership with Boehringer Ingelheim GMBH to develop a custom sensor for its Respimat inhaler. Propeller provides an FDA cleared digital health platform for chronic respiratory disease. In conjunction with the collaboration, the data collected will be wirelessly transmitted to GSK. The company is backed by Safeguard Sciences, the California HealthCare Foundation, the Social & Capital Partnership, and Walgreens, which have invested over $23mm to date. Propeller’s platform is currently used in over 35 commercial programs in the US and is compatible with the majority of inhalers. The device has received FDA 510(k) Class II clearance.

MEDTRONIC PLC SAMSUNG ELECTRONICS CO. LTD. SAMSUNG ELECTRONICS America INC. Medtronic PLC and Samsung Electronics America Inc. are partnering to develop digital health devices to help neumodulation patients and their health care providers. (Dec.)

Neuromodulation therapy involves the targeted delivery of electrical pulses and pharmaceuticals to specific CNS sites. Medtronic’s neuromodulation business – part of its restorative therapies group, which accounts for $6.8bn, or about a third of the company’s annual sales – makes neurostimulation devices and implantable drug delivery systems. The deal leverages Medtronic’s expertise in this field with Samsung’s proficiency in consumer electronics, digital media, and information technologies. The collaboration’s goal is to develop Android-based tools capable of wirelessly receiving/delivering real-time health data from Medtronic devices to improve patient and physician interactions. The partnership aims to provide patients suffering from chronic pain, movement disorders, incontinence, and other conditions with access to mobile technologies so they can transmit data (via smartphones, wearables, or tablets) to their physician to better manage therapy regimens and track and monitor symptoms. In June 2015, the companies signed a similar partnership in diabetes.

TOSHIBA CORP. TOSHIBA America MEDICAL SYSTEMS Inc. ZIEHM IMAGING INC. Toshiba America Medical Systems Inc. and Ziehm Imaging Inc. are teaming up to provide each other’s mobile C-arms for interventional and surgical cardiovascular imaging in the US. (Dec.)

Mobile C-arms are used in interventional and surgical imaging. Ziehm will offer Toshiba’s Infinix line, which offers clear and fast vascular and cardiac imaging for use in complex procedures. Toshiba’s products also have applications in neurology and combined angiographic and CT imaging. Ziehm’s mobile C-arm technology offers flexibility, efficiency, and advanced safety features, which will allow Toshiba to provide the right imaging and treatment for their patients.

Financings /Medical Devices CROYLIFE INC. To finance its acquisition of private heart valve firm On-X Life Technologies Inc., CryoLife Inc. received a commitment from Capital One, Fifth Third Bank, and Citizens Bank for a five-year senior secured facility, consisting of a $75mm term loan and a $20mm revolving credit facility. (Dec.)

HARVARD APPARATUS REGENERATIVE TECHNOLOGY INC. Harvard Apparatus RegenerativeTechnology Inc. entered into a two-and-a-half-year $15mm common stock purchase agreement with Aspire Capital Fund LLC. The company has completed an initial sale of 500k shares at $2. Proceeds will be used to fund research, development, and commercialization activities. HART recently received promising results on its Gen2 implants. (Dec.)

NEUROMETRIX INC. NeuroMetrix Inc. grossed $13.8mm in a preferred stock private placement of 13.8k Series C convertible preferred shares at $1,000. (Dec.)

Investment Banks/Advisors: Rodman & Renshaw Capital Group Inc.

SEASPINE HOLDINGS CORP. SeaSpine Holdings Corp. (surgical devices for spinal disorders) secured a $30mm credit facility with Wells Fargo Capital Finance. The loan has a term of three years with the option to be extended an additional one year. The facility bears a floating annual rate based on monthly average borrowings, ranging from 1.25% to 1.75% for base rate loans and LIBOR + 2.25% to LIBOR + 2.75% for LIBOR loans. Proceeds will support product launches, expansion of SeaSpine’s orthobiologics manufacturing, and potential future acquisitions. (Dec.)

MERGERS & ACQUISITIONS /Pharmaceuticals ASTRAZENECA PLC ACERTA PHARMA BV AstraZeneca PLC is further strengthening its blood cancer assets by acquiring a 55% stake in three-year-old private biopharma Acerta Pharma BV. Total consideration for the initial stake is $4bn, with $2.5bn payable up front and the remainder within the next three years. (Dec.)

Acerta’s key asset is acalabrutinib (ACP196), an oral Bruton's tyrosine kinase (Btk) inhibitor in Phase III trials for chronic lymphocytic leukemia and Phase II for other blood cancers and solid tumors. Regulatory submissions are expected during the second half of 2016, the further $1.5bn payment from AZ is due upon receipt of regulatory approval for any indication in the US or at the end of 2018, whichever comes first.
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HOT TOPICS:

- BUSINESS AND R&D
  - R&D Reorganization
  - Oncology Drug Pricing
  - Personalized Medicine
  - Companion Diagnostics
  - Rare Disease

- HOT MEDICAL AREAS
  - Oncology
  - Hepatitis C

- POLICIES ON DRUG REVIEW
  - FDA’s Breakthrough Designation and Other Expedited Pathways
  - Biosimilars
  - European Health Technology Assessment
  - FDA’s Budget And Top Officials

- REIMBURSEMENT
  - Commercial Formulary Controls
  - Federal 340B Discounts
  - Medicare Drug Rebates
  - Health Reform’s Impact On Drugs

- OTHER FDA ISSUES
  - Biopharma’s Use Of Social Media
  - Generic Drug User Fees

- MISCELLANEOUS
  - Medication Adherence
  - Comparative Effectiveness Research

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AZ also holds an option to acquire the remaining 45% of Acerta for an additional payment of $23bn (net of certain costs, incurred payments, and future adjusting terms). Acalabrutinib is a next-generation Btk inhibitor, making it a promising therapy for patients who are intolerant to first-generation options (including AbbVie’s /J&J’s Imbruvica (ibrutinib)) due to negative side effects. It also demonstrates positive results when used in combination with immunotherapies such as pembrolizumab (Merck’s Keytruda). AZ’s Medimmune unit developed the PD-L1 inhibitor durvalumab (MEDI476), which Celgene licensed rights to earlier this year. The investment in Acerta comes at a busy time for AZ, a day prior, the Big Pharma announced that it will pay $575mm for a portfolio of respiratory medicines from Takeda, and last month, it bought hyperkalemia drug developer ZPHarma for $2.7bn.

Investment Banks/Advisors: Goldman Sachs & Co; Jefferies & Co Inc. (Acerta Pharma BV)

ASTRAZENECA PLC
TAKEDA PHARMACEUTICAL CO. LTD.

AstraZeneca PLC paid $575mm for Takeda Pharmaceutical Co. Ltd.’s respiratory drug business. The transaction includes the transfer of 200 employees to AZ. (Dec.)

Takeda divested the unit so that it can continue to allocate more resources toward its four core areas of gastroenterology, oncology, CNS, and cardiovascular/metabolic. AZ, on the other hand, is building in respiratory, having also bought Almirall’s respiratory operations (including the marketed COPD drugophilia (aclidinium) plus preclinical Phase-III candidates) in 2014 and Pearl Therapeutics, which had the Phase III COPD program PT003 (formoterol and glycopyrrolate), in 2013. In addition, earlier this year AZ got US and Canadian rights to Actavis’ (now Allergan’s) branded respiratory drugs. AZ’s respiratory sales—driven by Symbicort (budesonide and formoterol) and Pulmicort (budesonide)—are only projected to grow at a 0.8% CAGR from 2014-2024 (from $5.1bn to $5.5bn) according to Datamonitor, and the company’s recent deals could potentially improve that growth. The current transaction includes Daxas/Dali-resp (roflumilast), a PDE4 inhibitor for COPD, Alvesco (ciclesonide), an inhaled corticosteroid for asthma, Omnans (ciclesonide) for allergic rhinitis; regional and local products, and preclinical candidates. Regarding Daxas, AZ already held the North American license from Actavis, which had rights to the product via a 2009 deal between Forest (acquired by Actavis) and Nycomed (owned by Takeda and called Takeda Pharmaceuticals International GBMHI). The present agreement now gives AZ full ownership of Daxas, and, as a result, the company is no longer responsible for royalty payments in the US. Sales for Daxas (excluding those for AZ in the US), Alvesco, and Omnans totaled $198mm for FYE March 2015.

BOEHRINGER INGELHEIM GMBH
SANOFI

Sanofi and Boehringer Ingelheim GmbH entered into exclusive discussions surrounding the swap of key businesses that could make Sanofi the number one consumer health care (CHC) firm in the world and help Boehringer become the second largest animal health company globally. (Dec.)

The partners are contemplating an exclusive business swap in which Sanofi would hand over its animal health business Merial to BI in exchange for BI’s CHC business (excluding the firm’s China unit).

If completed, Boehringer would pay Sanofi €4.7bn ($5.16bn) in cash. Currently the eighth largest in the world (with estimated 2015 revenues of €1.6bn), BI’s CHC offerings include lead products Bucaplan (antispasmodic); the laxative Dulcolax; Pharmaton, a multivitamin; cough treatments Muscosolvan and Bisolvon; and cold therapy Mucosaing/Lysopaine. The brands are all highly complementary to Sanofi’s existing CHC products such as the allergy treatments Allegra and Nasocit; digestive aids Motasol, Esensitive, and Enteroxemina; and the pain killers Dalprof, No-Spa, and Dorflex. Pro forma, Sanofi could see sales of €5.1bn, with a strongly enhanced presence in Germany and Japan, where the Big Pharma’s CHC exposure is limited. Boehringer Animal Health could see pro forma revenues of €3.8bn (up from €1.13bn in 2014) through the addition of Merial’s offerings in pet care, farm animal health, and veterinary public health.

CYTOS BIOTECHNOLOGY AG
KUROS BIOSURGERY AG

Public Swiss firm Cytos Biotechnology Ltd. and closely held Kuros Biosurgery AG are merging to create leading biosciences company in the tissue repair and regeneration space. (Dec.)

Each Kuros share will convert into 27 newly issued Cytos shares, and existing options and conversion rights for Kuros shares will be rolled over into comparable rights for Cytos shares. Post-transaction, Cytos and Kuros will have 20%/80% ownership, respectively, in the combined firm, which will operate as Kuros Biosciences AG. Kuros’s current top executives will retain their roles, and the board will be led by Cytos’ chairman and have representation from both firms. Kuros has two biomaterial platforms—one based on fibrin sealants, and the other based on a proprietary synthetic technology that mimics fibrin. Leading its pipeline is KUR023, a biomaterial designed to seal the dura following brain and spinal surgery. Next in line is the orthobiologic candidate KUR111, which has completed Phase IIb for bone fractures. Its third program, KUR113, is also an orthobiologic that’s completed Phase II. Kuros recently closed a $20mm financing to support CE mark approval for KUR023 and move KUR111 into US Phase III trials. Cytos brings to the table preclinical CYT003, which was created using the firm’s bacteriophage Q beta-derived virus-like particle (VLP) technology. A few months ago Cytos licensed Checkmate Pharmaceuticals exclusive rights to the VLP vaccine technology and CYT003 in exchange for $90mm in development milestones and double-digit royalties. Checkmate will study the candidate for cancer. Under a January 2015 tie-up, OnCore Biopharma (now part of Arborus Biopharma) has exclusive rights to the VLP platform in a deal worth up to $402mm in development milestones and $120mm in sales milestones, plus double-digit royalties. OnCore can explore the technology in six potential infectious diseases including hepatitis B but excluding influenza. These deals will remain in place once the merger closes. Cytos had been studying CYT003 in Phase IIb clinical trials for asthma but those studies were terminated in April 2014 because it didn’t meet a primary endpoint.

HORIZON PHARMA PLC
CREALTA PHARMACEUTICALS LLC

Horizon Pharma PLC is paying $510mm in cash for two-year-old specialty pharma Crealta Pharmaceuticals LLC. (Dec.)

Crealta’s key product, Krystexxa (pegloticase), is the only FDA-approved treatment for chronic refractory gout, a type of arthritis caused by excess uric acid in the blood. Crealta got the drug through its $120mm late-2013 acquisition of Savient Pharmaceuticals following a court-approved auction. Horizon will sell Krystexxa using its seasoned sales force having expertise in rheumatology and orphan diseases. The drug will fit nicely into Horizon’s portfolio which includes Rayos (prednisone) for inflammatory conditions including arthritis and the osteoarthritis drug Pennsaid (diclofenac). Crealta has one other product, Migerent (ergotamine tartrate and caffeine suppositories), which is sold for treating migraines. Investment Banks/Advisors: Jefferies & Co. Inc. (Horizon Pharma PLC)

IBA MOLECULAR INC.

SK Capital Partners entered into a definitive agreement to acquire IBA Molecular from CapVest Partners LP. The acquisition is expected to close by the end of Q1 2016. The company was jointly owned by SK Capital and Ion Beam Applications SA. (Dec.)

IBA Molecular develops, manufactures and distributes radiopharmaceutical products and services for molecular imaging in Europe and Asia. The company has a pipeline of diagnostic and therapeutic tracers for personalized medicine. IBA also provides educational, technical and marketing support. In August 2015 IBA sold its US operations to Illinois Health & Science, a non-profit health care system.

LIGAND PHARMACEUTICALS INC.
OPEN MONOCLONAL TECHNOLOGY INC.

Ligand Pharmaceuticals Inc. bought private antibody discovery company Open Monoclonal Technology Inc. (OMT; mAb platform using transgenic rats and mice) for $178mm in cash and stock. (Dec.)

Ligand will pay approximately $92.6mm in cash and issue $85.4mm million in Ligand common stock (about 790k shares). OMT was founded in 2008 by Roland Buelow, PhD, its current CEO, who will stay on after the acquisition as VP, Antibody Technologies. The company’s OmnAb platform involves the genetic engineering of animals for the generation of naturally optimized monoclonal, bispecific, and polyspecific human therapeutic antibodies and includes three transgenic rodent models. OmnRat (mAb technology based on rats including a complete immune system to produce antibodies with human idiotypes), OmniMouse (transgenic mice that complement OmnRat and expand epotope coverage), and Omniplic (a fixed light chain designed for the development of bispecific fully human antibodies). OMT says all antibodies generated through these platforms have high affinity, specificity, expression, solubility, and stability thereby providing partners with more rapid discovery capabilities. OMT has 16 OmnAb alliances with Big Pharmas such as Amgen, J&J, Janssen, and Pfizer, first-tier biotech Celgene, and various other biopharma companies including Genmab, WuXi, and most recently Seattle Genetics, which just last month gained rights to the platform for development of oncology antibody-drug conjugates. Along with the OmnAb technology suite, Ligand is also getting these 16 fully funded partnerships and antibody-specific licenses; these alliances have been structured similarly to Ligand’s licenses for its Captisol drug formulation technology with a combination of up-front license payments, annual technology access fees, development and commercialization
milestones, and royalties (typically in the low-to-mid-single digits). Ligand anticipates OMT’s licensing deals could generate over 30 clinical candidates in the next 10 years. Ligand also predicts three antibodies from the OMT platform will be in Phase I by the end of 2017, and expects as many as 15 antibodies could enter the clinic (or potentially be more advanced) by 2020. The transaction is projected to add 5% to Ligand’s 2016 revenue (which is forecasted between $113-117mm, including $6mm in sales from the OMT business) and 7-10% to its annual revenue over the next decade, plus potential royalties from existing deals.

Alliances
/Pharmaceuticals

AKEIA THERAPEUTICS INC. MITSUBISHI CHEMICAL HOLDINGS CORP. Mitsubishi Tanabe Pharma Corp.

Akeia Therapeutics Inc. granted Mitsubishi Tanabe Pharma Corp. exclusive rights to develop and sell vadadustat (formerly AK8654B) for anemia related to chronic kidney disease (CKD) in Japan, Taiwan, South Korea, Singapore, Malaysia, India, Indonesia, East Timor, Mongolia, the Philippines, Vietnam, Laos, Cambodia, Thailand, Brunei, Myanmar, Nepal, Sri Lanka, Bangladesh, Bhutan, Maldives, Palau, and Tonga. (Dec.)

Mitsubishi Tanabe pays $40mm up front, $60mm in funding related to a global Phase III program, and up to $250mm in development and sales milestones, plus tiered royalties from the low teens up to 20%. Phase II vadadustat is a once-daily oral hypoxia-inducible factor prolyl hydroxylase inhibitor that raises hemoglobin levels and improves iron mobilization in CKD patients with anemia. The compound originated at Procter & Gamble, but was handed off to spin-out Akeia when P&G dismantled its pharma business in the mid-2000s.

AMGEN INC. MERCK & CO. INC.

Amgen Inc. and Merck & Co. Inc. are teaming up to conduct a Phase Ib/II safety and efficacy trial of Amgen’s CD19 antagonist Blinostic (blinatumomab) in combination with Merck’s PD-1 receptor antagonist Keytruda (pembrolizumab) in patients with diffuse large B-cell lymphoma (DLBCL). (Dec.)

Amgen sells Blinostic for acute lymphocytic leukemia, and is currently studying the therapy in Phase II for B-cell lymphoma. Keytruda is sold as a treatment for melanoma and non-small cell lung cancer, but is also in various stages of development for many other cancers. The firms also agreed to perform a Phase II trial of Amgen’s colony-stimulating factor 1 receptor antagonist AMG820 with Keytruda in patients with select advanced solid tumors, including non-small cell lung, colorectal, and pancreatic cancers. AMG820 is currently in Phase I for unspecified solid tumors.

ARISIA THERAPEUTICS INC. BIOGEN INC.

Arisia Therapeutics Inc. and Biogen Inc. are teaming up to develop subcutaneously administered hemophilia treatments as an alternative to the current intravenous therapies. (Dec.)

Biogen will have access to Arisia’s patented formulation technology, which can create high-concentration, low-viscosity subcutaneous dose formulations of protein and antibody drugs. In return, Arisia gets an up-front payment, up to $100mm in development, regulatory, launch, and sales milestones, plus royalties. Biogen sells two hemophilia drugs, Eltrecote and Alprolix, both infusions. The development of subcutaneous therapeutics will allow hemophilia patients to better adhere to their treatments, which are currently dosed via IV.

ASTELLAS PHARMA INC. Agenys Inc. BELLICUM PHARMACEUTICALS INC.

Astellas Pharma Inc.’s Agenys Inc. subsidiary licensed Bellicum Pharmaceuticals Inc. worldwide rights to use its technology to develop and commercialize cell therapies, including chimeric antigen receptor T-cell (CAR-T), for tumors expressing the prostate stem cell antigen (PSCA). (Dec.)

Agenys receives an up-front fee, clinical and sales milestones, and single-digit sales royalties. Astellas or Agenys keeps an option to commercialize in Japan any PSCA-targeting drug developed with Bellicum’s CART cell technology. Upon exercise, Bellicum would get an option fee and royalties, and the milestones due to Astellas would be reduced. The PSCA antigen is expressed in various cancer types including prostate, pancreatic, bladder, esophageal, and gastric. Bellicum will use the licensed IP to continue developing its preclinical pancreatic cancer candidate BPX601. The candidate was created using the company’s GoCAR-T technology in which an MC (MyD88/CD40) molecular switch enables pharmacologic control over the activation, proliferation, and persistence of the GoCAR-T cells in a patient. Bellicum plans to move BPX601 into the clinic in H1 2016.

ASTELLAS PHARMA INC. BIOVISTA INC.

Biovista Inc. will use its Clinical Outcome Search Space (COSS) technology to identify new indications for some undisclosed Astellas Pharma Inc. compounds. (Dec.)

Terms of the deal weren’t disclosed. The COSS systematic discovery platform identifies correlations between drugs, targets, pathways, adverse events, and diseases. The information can be used to make informed decisions about a drug’s development, thus help improve the chances of its success. Biovista has similar agreements with Pfizer (November 2010) and Novartis (April 2011). Both those deals involved up-front money and milestones.

AVEO PHARMACEUTICALS INC. EUISA PHARMA

Aveo Pharmaceuticals Inc. (also known as Aveo Oncology/B-A) granted EUISA Pharma exclusive rights to develop, manufacture, and sell its Phase II VEGF inhibitor tivozanib for renal cell carcinoma and potentially other indications in Europe, Latin America (excluding Mexico), Africa, Australasia, and New Zealand. (The deal excludes Russia, Ukraine, and the CIS, where Pharmstandard holds rights under a deal signed earlier this year, and also excludes non-cancerous diseases and conditions of the eye.) (Dec.)

Aveo got tivozanib from Kirin Brewery (now Kyowa Hakko Kirin) in 2007, and in 2011 Aveo granted Astellas global rights. Following the FDA’s rejection for regulatory approval of the compound, Astellas pulled out of the deal in 2014 and all rights returned to Aveo. Ophthotech has since taken rights to develop it for all non-oncology ophthalmic indications (in late 2014), and Pharmstandard got its license (in the oncology area) earlier this year. Under the current deal, Aveo could see a total of up to $400.5mm, plus tiered royalties ranging from the low-double-digits to the mid-twenties. (A percentage of all milestones and royalties will go to Kyowa.) EUISA pays $2.5mm in R&D money up front, with an additional $20mm in R&D funding due if the company decides to use Aveo’s Phase III data relating to third-line RCC. (After its rejection, the FDA told Aveo earlier this year that it could investigate the project’s use for third-line RCC based on a new trial design.) Aveo may also receive $2mm in research funding if EUISA chooses to run a Phase I combination study of tivozanib with a checkpoint inhibitor. A variety of regulatory milestones are also possible. EUISA could pay $4mm upon EMA marketing approval, $2mm per country upon reimbursement approval in each of France, Germany, Italy, Spain, and the UK, and $2mm each for marketing approval in three out of five specific countries (Argentina, Australia, Brazil, S. Africa, and Venezuela). Aveo is also eligible for $2mm if EUISA files for EMA marketing approval in each of up to three additional indications and $5mm each per indication when marketing approval comes through for up to three more indications, plus up to $335mm in sales milestones. EUISA funds all regulatory and commercialization activities; the company’s initial plan is to file for marketing authorization approval with the EMA as first-line treatment for advanced RCC during the first quarter of 2016.

BAVARIAN NORDIC AS JOHNSON & JOHNSON Jansen Pharmaceuticals Inc.

Bavarian Nordic AS licensed Janssen Pharmaceuticals Inc. exclusive rights to use its MVA-BN (Modified Vaccinia Ankara - Bavarian Nordic) technology to develop a heterologous prime-boost vaccine for human papillomavirus. (Dec.)

Janssen will use MVA-BN in conjunction with its own AdVac to create a vaccine that can target all cancers induced by HPV. Janssen will fund and perform all clinical development, registration, distribution, and commercialization activities worldwide. Bavarian Nordic is responsible for all manufacturing related to MVA-BN. Bavarian Nordic receives $9mm up front, up to an additional $116mm in development and commercial milestones, and tiered single-digit sales royalties. Prime-boost vaccines have a stronger and longer-lasting immune response due to increased antibodies and T-cell responses. The parties seek to create vaccines that can treat HPV-related cancers and not just prevent them. The deal builds on an October 2014 tie-up under which Bavarian Nordic licensed Janssen’s Crucell Holland BV subsidiary exclusive worldwide rights to its MVA-BN Filovirus vaccine candidate for the Zaire and Sudan strains of Ebola and the related condition Marburg disease. That collaboration has resulted in a Phase III Ebola vaccine candidate combining MVA-BN with AdVac.

BAYER AG

Bayer HealthCare Pharmaceuticals AG BAYER-CRISPR JV CRISPR THERAPEUTICS

Bayer HealthCare Pharmaceuticals AG and CRISPR Therapeutics formed a 50/50 joint venture tasked with finding cures for blood disorders (including hemophilia), blindness, and congenital heart disease. The Bayer LifeScience Center (BLSC), a new R&D innovation unit at Bayer, help set up the JV, which will focus on
DEALMAKING

BIO TASK SND BHD
INNOVUS PHARMACEUTICALS INC.

Innovus Pharmaceuticals Inc. granted Bio Task SND BHD exclusive rights to sell five of its sexual health products in Malaysia. Bio Task made an up-front payment and is responsible for an agreed-upon transfer price and up to $34mm in sales milestones. (Dec.)

Bio Task, which was previously mainly in the diagnostics business and didn’t appear to have any pharma or OTc products in its portfolio, will now detail the following products to the B50 gynecologist offices that its sales force visits: Zestra, to increase arousal and sexual desire in women; EjectDelay for premature ejaculation; Sensum+ for increasing penile sensitivity; Vesile for increasing sexual and cognitive health; and Zestro Glide, a high viscosity water-based lubricant. The alliance marks the eleventh commercial partnership for Innovus, which now benefits from deals for its products in 61 countries worldwide.

BIOATLA LLC
PFIZER INC.

BioAtla LLC and Pfizer Inc. are teaming up to cross-license each other’s antibody assets. (Dec.)

Pfizer is contributing antibody drug conjugates (ADCs), which include a payload and a delivery system that allows the payload to attach to a cell. BioAtla is handing over conditionally active biologic (cAB) antibodies, which can be activated in the presence of antigens based on the physiological conditions of the microenvironment. The parties seek to develop CAb-ADCs that can more safely deliver cancer drugs to the diseased cell and not healthy tissue, offering improved treatments for patients with a variety of cancer types. BioAtla and Pfizer will split development and commercialization rights, with each eligible for milestones and royalties. The Big Pharma also gets an exclusive option to license BioAtla’s CAB project that targets the protein CTLA-4, an immune checkpoint that hampers the body’s ability to detect cancer. Under the agreement, BioAtla stands to receive as much as $1bn in up-front, regulatory, and sales milestones, plus tiered marginal sales royalties reaching double digits. The deal further strengthens Pfizer’s pipeline in immune-oncology, a hot area of focus over the last couple years. In November 2014, the firm licensed from Merck a PD-L1 antagonist, avelumab, which is currently in Phase III trials.

BRISTOL-MYERS SQUIBB CO.
GLAXOSMITHKLINE PLC

ViiV Healthcare

GlaxoSmithKline PLC’s ViiV Healthcare acquired early- and late-stage HIV candidates from Bristol-Myers Squibb Co. (Dec.)

The deal is structured in two parts. ViiV will acquire the late-stage assets for $317mm up front, $518mm in development and regulatory (first commercial sale) milestones, $750mm in sales milestones for each drug, and tiered royalties. In this transaction, ViiV gets Phase III fostemsavir (BMS663068), an HIV attachment inhibitor/GP120env antagonist that has a 62% likelihood of approval according to BioMedTracker, 1% above average due to Phase IIb results in treatment-experienced HIV-1 patients that showed fewer adverse events compared with BMS’s marketed product Reyataz (atazanavir) plus ritonavir. A regulatory filing is expected in 2018 (the candidate has breakthrough therapy designation). ViiV also received the maturation inhibitors BMS955176 (Phase IIb, for treatment-naive and treatment-
experienced patients) and BMS986173. In the second transaction, Viv pays $33m up front, up to $587m in development and regulatory (first commercial sale) milestones, $700m in sales milestones for each product, and tiered royalties for discovery and preclinical programs including BMS986197, a biologic that inhibits maturation, integrase, and capsid. Viv will offer jobs to 20 BMS drug discovery scientists. Viv is responsible for managing and resourcing the programs, while BMS will provide R&D support, paid for by Viv. Viv is a joint venture that is majority owned by GSK and minority owned by Pfizer and Shionogi. It already markets 12 HIV products, and may pursue combinations with the newly acquired candidates. Earlier this year, Viv and Janssen agreed to develop a combination of the former’s integrase inhibitor Tivicay (dolutegravir) and latter’s non-nucleoside reverse transcriptase inhibitor Edurant (rilpivirine). (Tivicay and BMS630686 could be one of the potential new combinations, according to GSK.) BMS didn’t completely exit the HIV market via the deal with Viv. While it ended virology drug discovery two years ago, BMS still retains ownership of the launched medicines Reyataz, Evotaz, Sustiva, and Atripla. Together, the company is making a push toward more specialty drugs, including in the areas of immuno-oncology and fibrosis, and lessening focus on primary care.

BRISTOL-MYERS SQUIBB CO. NEON THERAPEUTICS

Neon Therapeutics and Bristol-Myers Squibb Co. agreed to test a combination of the former’s personalized neoantigen vaccine NEOPV01 and latter’s Opdivo (nivolumab). (Dec.)

In Phase Ib the partners will review the safety, tolerability, and preliminary efficacy of the combination in melanoma, smoking-associated non-small cell lung cancer, and bladder cancer. They will also test neoantigen-specific immune responses in peripheral blood and tumor tissues, and measure PD-L1 expression. Neon is responsible for conducting the trial at multiple US sites starting in 2016. The biotech’s NEOPV01 contains neoantigens – which are expressed on tumors or cells infected with an oncolytic virus – taken directly from the patient. Neoantigen vaccines target the patient’s individual immunologic mutations within the tumor’s DNA. NEOPV01 is in preclinical studies for melanoma, glioblastoma, smoking-associated non-small cell lung cancer, and bladder cancer. Neon recently licensed technology related to the neoantigen vaccines from Massachusetts General Hospital, Dana-Farber Cancer Institute, and the Broad Institute. Bristol’s antibody Opdivo (nivolumab), a PD-1, PD-L1, and PD-L2 inhibitor, is approved for melanoma, non-small cell lung cancer, and, most recently, renal cell cancer, and is in Phase I-III trials for multiple solid and hematological cancers.

CARDIOIME PHARMA CORP.

CHONG KUN DANG PHARMACEUTICAL CORP.

Cardiome Pharma Corp. licensed Chong Kun Dang Pharmaceutical Corp. exclusive rights to market its intravenous Brinvas (vernakalant) for atrial fibrillation in South Korea. (Dec.)

Chong Kun is responsible for obtaining regulatory approval and commercializing the drug in its home territory of South Korea, where a launch is anticipated for 2017. Brinvas is indicated for rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults. Cardiome has several licensing agreements for the product including a pact with EddingPharm International for marketing in the Asian countries of China, Taiwan, and Macau. Brinvas is sold in 32 countries worldwide. Chong Kun recently partnered with NeoVacs SA to market a lupus and dermatomyositis therapy, and S1 Biopharma for Loresys (bupropion and trazodone), a Phase Ib candidate for hypoaactive sexual desire disorder in women.

CELGENE CORP.

INCEPTION IBD INC.

Celgene Corp. is partnering with Inception IBD Inc. and has the option to acquire the one-year-old firm at the end of the collaboration. (Dec.)

Celgene will provide Inception IBD with up to $40m in cash, which the start-up will use to move its small-molecule ulcerative colitis and Crohn’s disease candidates from the discovery-stage through preclinical studies. Inception IBD, which currently raised $14.1m in Series A financing fromVersant Ventures, Fonds de solidarité FTQ, and Insum Transfer Initia- tive, identifies compounds using its translational platform and genomic targets identified from analyz- ing tissue of IBD patients. These competencies can help the firm focus on the key disease factors such as dysfunction of the epithelial barrier. Inception IBD is one of six firms incubated by Inception Sciences Inc. since 2011.

CHONG KUN DANG PHARMACEUTICAL CORP. NEOVACS SA

NeoVacs SA licensed Chong Kun Dang Pharmaceuti- cal Corp. exclusive rights to market in South Korea the interferon-alpha kinoid vaccine for lupus and dermatomyositis. (Dec.)

NeoVacs will receive €1m ($1.1m) up-front, pos- sibly another €4m in pre-sales milestones, plus royalties. NeoVacs will supply Chong Kun with the finished product and receive a margin within the transfer price. The IFN-alpha kinoid is currently in Phase Ib. Chong Kun expects to begin the registra- tion process in South Korea by the end of 2017, with a launch anticipated in early 2018. NeoVacs chose Chong Kun as a partner because of its strength in established partnership with doctors treating lupus patients.

CHONG KUN DANG PHARMACEUTICAL CORP.

S1 BIOPHARMA INC.

S1 Biopharma Inc. granted Chong Kun Dang Pharmaceu- tical Corp. (CKD) rights to commercialize its sexual dysfunction therapy Loresys (bupropion/ trazodone) in South Korea, once approved. (Dec.)

CKD is responsible for up-front and milestone payments, plus royalties. It also gets right of first refusal for future sales agreements related to ad- ditional indications. S1 completed Phase Iia trials with Loresys in women with hypoaactive sexual desire disorder, and is preparing the therapy for Phase Iib. It is an oral non-hormone treatment that works by restoring normal levels of the neurotrans- mitters dopamine, serotonin, and norepinephrine to regulate sexual inhibition and excitation. CKD looks forward to the international exposure it gains through the deal as it plans future global marketing collaborations for Loresys.

COUR PHARMACEUTICAL DEVELOPMENT CO. INC.

TAKE DA PHARMACEUTICAL CO. LTD.

Takeda Pharmaceutical Co. Ltd. and Cour Pharma- ceutical Development Co. Inc. partnered to develop treatments for celiac disease and other gastrointestinal conditions based on Cour’s immune-based technol- ogy. (Dec.)

The companies will focus on nanotechnologies using Cour’s Tolerizing Immune Modifying nanoParticle (TIMP) platform, which consists of a polymer and antigenic proteins which are encapsulated and delivered intravenously. Takeda and Cour will concen- trate on TIMP compounds for celiac disease, in hopes of developing a therapy that will allow patients to digest gluten while controlling gluten-reactive T-cells. Cour gets money up front plus milestones. If Takeda exercises an option to license the celiac compound after Phase Ila, it will pay royalties. (Takeda has an additional option to license up to three more TIMP compounds, which would result in additional development, regulatory, and sales milestones, plus royalties.) The deal could strengthen Takeda’s Gipline which includes Phase III Enyvio (vedolizumab) for ulcerative colitis and Crohn’s disease, and TAK114, in Phase II for ulcerative colitis.

EASTON PHARMACEUTICAL CO. LTD.

XL-PROTEIN GMBH

XL-protein GMBH and Easton Pharmaceutical Co. Ltd. are partnering to develop long-acting biophar- maceuticals for ophthalmic and potential other indications. (Dec.)

XL-protein will use its PASylation technology, which can extend a compound’s half-life, on a target provide by Easton. XL-protein will conduct early preclinical studies. Easton will take over further development and manufacturing and gets exclusive rights to market any resulting drugs in its home territory of China. It also has executive options to license worldwide rights and rights for additional indications. XL- protein receives an up-front payment; preclinical and clinical development, regulatory, and commercial milestones; and tiered, mid-to-mid-high single digit sales royalties. Half-life extension results in a reduction in dosing frequency and lower drug costs.

GALAPAGOS NV

GILEAD SCIENCES INC.

A few months after losing a major partner for the project, Galapagos NV has penned a new deal for its Phase II rheumatoid arthritis and Crohn’s disease compound filgotinib, granting Gilead Sciences Inc. global rights to develop, manufacture, and sell the therapy. (Dec.)

Abbott licensed rights to the JAK1 inhibitor back in 2012, and its spin-off AbbVie took over the deal in 2013. However, earlier this year AbbVie made the decision to instead focus on its own similar in-house candidate and returned all rights to Galapagos. (Galapa- gos could have seen up to $1bn in milestones from that deal, in addition to money that had already been shelled out by Abbott.) Gilead now pays $725mm up front ($300m in cash and a $425mm equity invest- ment), purchasing 6.7mm Galapagos shares (a 15% front ($300mm in cash and a $425mm equity invest- ment), purchasing 6.7mm Galapagos shares (a 15%)}
DEALMAKING

sales activities. Galapagos holds onto an option to co-promote in the UK, Germany, France, Italy, Spain, Belgium, the Netherlands, and Luxembourg. If it exercises the option, profits in those territories will be split equally. If it co-promotes in Belgium, the Netherlands, or Luxembourg, Galapagos books those sales.)

A growing pool of large firms that are using Enhance in their development programs, including Roche, AbbVie, Janssen, Baxalta, and Pfizer. (Just last month, Halozyme received a $1mm milestone when Pfizer closed the first patient in a Phase I trial of an Enhance-formulated version of rvpansel for sickle cell anemia.)

INTREXON CORP.

GALÈNA BIOPHARMA INC.

MIDATECH PHARMA PLC

To focus efforts on its cancer immunotherapy development pipeline, Galéna BioPharma Inc. has sold off its US rights to the anti-emet McZuplen (ondansetron) to Midatech Pharma PLC. (Dec.)

Galéna originally licensed US rights to the therapy from MonoSolRx in 2014. Midatech now pays Galéna a total of up to $29.75mm ($3.75mm up front and $26mm in sales milestones), Galéna agreed to give $900k of the up-front to MonoSolRx, along with 20% of any milestone payments it receives. Zuplen is an oral ondansetron formulation for nausea and vomiting related to chemotherapy, radiotherapy, and surgery. It was approved by the FDA in 2010 and uses MonoSol Rx's PharmFilm oral soluble film technology. The therapy dissolves on the tongue in less than 30 seconds, making it an ideal option for patients who have trouble swallowing pills due to extreme nausea or oral irritation. The deal completes Galéna's mission to offload its commercial operations and focus solely on development activities. Last month, it sold Sentynl Therapeutics US rights to its Abstral sublingual fentanyl tablets; those rights originally came to Galéna from Orexo in 2013.

GLAXOSMITHKLINE PLC

ZYMEWORKS INC.

The two companies will work to further develop Zymeworks' Efferctor Function Enhancement & Control Technology platform (EFFECT) through testing of engineered Fc domains tailored to induce specific antibody-mediated immune responses. After the collaboration has ended, both companies will have the right to develop and commercialize the antibody candidates. Specifically, GSX will be allowed to develop a minimum of four candidates across multiple disease areas and Zymeworks will receive preclinical, clinical, and commercial milestones of $11mm per product plus tiered royalties on sales. The deal combines Zymeworks' antibody engineering expertise with GSX's drug discovery capabilities.

HALOZYME THERAPEUTICS INC.

ELI LILLY & CO.

Eli Lilly & Co. is the latest firm to license rights to use Halozyme Therapeutics Inc.'s Enhanze drug delivery platform in the development of its drug projects. (Dec.)

The specific compounds were not disclosed, but the deal includes up to five targets. Lilly paid $25mm up front and committed to $160mm in development, regulatory, and sales milestones per target, plus mid-single-digit royalties. Enhance is based on a patented recombinant human hyaluronidase enzyme (HDP-120) that temporarily breaks down hyaluronan – a key component of the extracellular matrix – to help with dispersion and absorption of subcutaneously delivered drugs that may previously have only been deliverable intravenously. Lilly joins a growing pool of large firms that are using Enhance in their development programs, including Roche, AbbVie, Janssen, Baxalta, and Pfizer. (Just last month, Halozyme received a $1mm milestone when Pfizer closed the first patient in a Phase I trial of an Enhance-formulated version of rvpansel for sickle cell anemia.)

INTREXON CORP.

JOHNSON & JOHNSON

Janssen Pharmaceutica NV

Intrexon Corp. is partnering with Janssen Pharmaceutica NV to discover and develop therapies for Type II diabetes, obesity, and other metabolic conditions associated with energy dysregulation. (Dec.)

Intrexon will use its ActoBiotics platform, which provides in situ expression and secretion of biotechnol ogy to generate engineered gut microbes that are designed to target various characteristics of Type II diabetes and improve efficacy in maintaining long-term glycemic control. Just four months ago, Intrexon teamed up with Synthetic Biologics to create ActoBiotics-generated compounds for phenylket onuria. Intrexon gained the platform through its February 2015 acquisition of ActoGeniX NV.

LIGAND PHARMACEUTICALS INC.

RODES INC.

Ligand Pharmaceuticals Inc. licensed Rodes Inc.'s global exclusive rights to three Captisol-enabled programs, two in the neurology field and one in the respiratory area. (Dec.)

Gained though its 2011 acquisition of CyDex Pharmaceu ticals, Ligand's Captisol technology is a chemically modified cyclodextrin derivative, engineered for safe administration; when linked to an IV or topical drug, it provides improved solubility, stability, and bioavailability of the active pharmaceutical ingredients. Rodes, which is focused on picking up all development and commercialization costs, will apply the Captisol platform to fosphenytoin, meloxicam, and budesonide/azelaione. Captisol-enabled (CE) fosphenytoin is a Phase III trial in intravenous (IV) and intramuscular (IM) an ticonvulsant for epilepsy. Pfizer's Cerebyx is currently sold in this same indication, but requires refrigeration; Rodes' CE version could be dispensed in vials, syringes, and pre-mixed bags. Meloxicam is an IV and IM Phase I-ready compound for post-surgical, trauma, and cancer pain used after administration of IV/IM NSAIDs and in place of opioids. Mobic, currently marketed by Boehringer Ingelheim for arthritis pain, is only available in an oral formulation. CE budesonide/azelaione is an intranasal formulation of a fixed-dose corticosteroid/antihistamine combination for allergic rhinitis, intended to improve compliance in once-daily and twice-daily dosing. The compound is in a Canadian Phase II proof-of-concept study and Rodes is preparing it for Phase I in the US. For each of the three programs, Rodes could pay Ligand development and commercial milestones, revenue from Captisol sales, and royalties of 8-11% on future net sales. This deal creates a pipeline for Rodes, which is aiming to establish a specialty pharmaceutical model.

MALLINCKRODT PLC

THE MEDICINES CO.

Mallinckrodt PLC paid $175mm in cash to buy three of The Medicine's Co.'s hemostasis brands. Up to an additional $235mm in milestones are payable in the future. (Dec.)

The deal includes Recothrom, a recombinant topical thrombin marketed in the US and internationally for minor bleeding; PreveLeak, a flexible surgical sealant indicated for use in vascular reconstruction procedures and marketed in the US and Europe; and Raplixa, a powder fibrin sealant made from human plasma-derived fibrinogen and thrombin and approved as an adjunct hemostatic for mild-to-moderate bleeding. Mallinckrodt will sell the products through its Specialty Brands Segment, and says that the acquisition enhances its hospital portfolio, which already includes IVMax (inhaled nitric oxide for hypoxic respiratory failure) gained through the company's acquisition earlier this year of Ikaria) and the Thenakos line of extracorporeal photophoresis systems. Mallinckrodt plans to promote Recothrom alongside its Orfrime (acetaminophen) for postsurgical pain.

NOVO NORDISK A/S

XOMA CORP.

Xoma Corp. licensed Novo Nordisk A/S exclusive worldwide rights to develop and commercialize its XMeta fully human allosteric monoclonal antib ody-d. (Dec.)

Xoma gets $5mm up front plus up to $250mm in development, regulatory, and commercial milestones, and mid-single-digit to high-single-digit sales royalties (Strategic Transactions estimates 4-9%). Xoma keeps commercial rights for rare disease indications such as endocrine disorders, but Novo Nordisk has an option to license those rights and, if exercised, it would make additional payments. Created using Xoma's ModuLX technology, XMeta has high-affinity antibodies are designed to selectively modulate/up-regulate the insulin receptor and have glucoregulatory activity. In preclinical studies they reduced hypoglycemia and weight gain. Because XMeta antibodies bind the insulin receptor at a different site than insulin, they don't significantly interfere with insulin binding. Xoma chose Novo Nordisk as a partner because it's a leader in diabetes treatments.

PIERIS PHARMACEUTICALS INC.

ROCHE

In its second immuno-oncology deal within days, Roche received worldwide rights to Pieris Pharmaceut icals Inc.'s Anticalins programs against an undisclosed cancer target. The agreement may be expanded to multiple targets. (Dec.)

Roche also recently teamed up with start-up SQZ to use the latter's CellSqueeze technology to engineer B-cells so that they induce the immune system to attack cancer. In the current agreement, Roche pays $6.4mm up front and up to $409.3mm in other various fees including R&D funding plus development, regulatory, and sales milestones (Pieris says the majority of the payments are for development milestones). In addition, it is responsible for mid-single-digit-to-low-double-digit royalties (Strategic Transactions assumes 5-29%). Pieris is in charge of discovery, characterization, and optimization of the Anticalins, and then the partners will review different drug formats through preclinical studies. The
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Big Pharma takes over iND-enabling tests, clinical trials, and marketing. Anticalins are lipocalin (protein) derivatives that Pieris has engineered so that they have high specificity and affinity for multiple targets. Anticalins also have the potential to be delivered via different formulations. While not specified, it’s possible that Roche and Pieris will develop a bi-specific therapeutic. Pieris is independently working on such an Anticalin that simultaneously targets HER2 and CD137. Pieris has already built a collaborative platform with larger pharma companies including Daiichi, Allergan, Takeda, and Sanofi, and the biotech says the deal with Roche is the first it’s done in the immuno-oncology arena. Allergan and Sanofi’s agreements focus on ophthalmology and infectious disease, respectively, while the others involve undisclosed targets.

**ROCHE**

Roche’s Biologics unit is collaborating on an alternative autologous cell therapy with NCI unit CellSqueeze from MIT. This is to work with an alternative autologous cell therapy and top biotechs including Novartis are working with a vascular adhesion protein 1 (VAP-1) inhibitor and commercialization rights to Novartis’s CellSqueeze against the cancer. The current alliance is Roche’s rights to CellSqueeze technologies (including full exercise of 231k warrants from the private placement of 4.1mm shares at $1.43 (a 17.2% discount)). The company raised $2mm through the private sale (to health care-focused institutional investors) at $4.50. Proceeds will fund development of ERY-ASP (GRASPA) for acute lymphoblastic leukemia and non-Hodgkin lymphoma, and will also go towards earlier pipeline projects and technology enhancements.

**SUPPORT TO ANIMALS**

Boehringer Ingelheim GmbH (BI) and MD Anderson Cancer Center entered into a collaboration for pancreatic ductal adenocarcinoma products. The partnership combines MD Anderson’s preclinical concept validation and clinical testing capabilities with BI’s innovative medicines for novel targets. The collaboration will be used to identify new therapeutic concepts and biomarkers and to develop breakthrough therapy medicines. Boehringer currently has BIB35220 in Phase I for pancreatic cancer and BIB36845 in Phase II trials.

**UPSHER-SMITH LABORATORIES INC.**

Upsher-Smith Laboratories Inc., a specialty therapeutic company, announced that it has licensed rights to sell Armune BioScience’s non-PSA blood test Apifyr for prostate cancer to certain medical professionals in the US. (Dec.)

**AETERNUM ZENTARIS INC.**

Aeterna Zentaris Inc. (oncology, endocrinology, and women’s health) netted $15.4mm through the public sale of 4.2mm common shares (including the overallotment) at $69. (Dec.)

**BIOPHARMX CORP.**

BioPharmX Corp. raised $5.9mm in a common stock private placement of 4.1mm shares at $1.43 (a 17.2% premium) from investment vehicles of Franklin Ad-

in various indications including IBS and inflammatory pain; it’s unclear which disease the partners will now target. Proximagen acquired the VAP-1 assets from Biovitrum (now Swedish Orphan Biovitrum) in 2009. The success of Proximagen’s VAP-1 inhibitors, particularly how well their revenues do, will influence approximately 57.5% of the undisclosed amount of earn-outs to which Proximagen is entitled as part of the Upsher-Smith Laboratories acquisition in 2012. Biotie has also been trying its luck with the anti-VAP-1 small molecule BTT1023 and the BTT1023 antibody, both in the inflammatory area, but Biotie has lost partners for each candidate. Roche turned down an option to license BTT1023 and Seikagaku had Asian rights to BTT1023 but returned the program because it no longer fit the company’s business strategy. Other potential competitors in the VAP-1 area include Astellas, Biopharmaxis, and R-Tech Ueno.

**FINANCINGS**

**/Pharmaceuticals**

**AEOLUS PHARMACEUTICALS INC.**

Aeolus Pharmaceuticals Inc. raised $67.7mm in a private placement from investors including BVF Partners Corp. BVF will purchase $4.5mm in preferred units consisting of 4,500 Series C convertible preferred shares, convertible into 20.5mm common shares and warrants for another 20.5mm common shares. Other investors will purchase a total of 10.2mm common shares at $0.22 per share (a 19% discount) along with 5-year warrants for another 10.2mm common shares exercisable at $0.22. Proceeds will be used for the development of AEO10150 for the pulmonary effects of acute radiation syndrome; human clinical trials of AEL10150 in idiopathic pulmonary fibrosis and radiation oncology; to complete preclinical development of AEL20415 for infectious diseases; and for AEO1114B for Parkinson’s. (Dec.)

**ICON PLC**

ICON PLC raised $350mm in a redeemable senior note private placement. The notes bear interest at 3.64% and are due in 2020 with interest payable semi-annually beginning in June 2016. The proceeds are expected to be used to refinance the company’s existing debt. (Dec.)

**KITE PHARMA INC.**

Kite Pharma Inc. (cancer immunotherapies) netted $273mm through the public sale of 4.2mm common shares (including the overallotment) at $69. (Dec.)

**MERRIMACK PHARMACEUTICALS INC.**

Merrimack Pharmaceuticals Inc. (cancer drug discovery) sold $175mm of its senior secured notes due 2022, for net proceeds of $168mm. (Dec.)

**NORTHWEST BIOThERAPEUTICS INC.**

Northwest Biotherapeutics Inc. (cancer immunotherapies) netted $117mm through the registered direct sale (to health care-focused institutional investors) of 3.5mm common shares at $3.60, a 15% discount. Buyers also received five-year warrants to purchase 1.75mm shares at $4.50. HC Wainwright was the placement agent. (Dec.)

**NUEVOlUTION AS**

Nuevaolution AS (small-molecule drug screening) completed an initial public offering in Sweden and Denmark of 14.2mm shares (including the overallotment) at SEK 17.50, resulting in gross proceeds of SEK250mm ($29.7mm), up-sized from the original
SEK225mm amount. The company has applied to trade its shares on Nasdaq’s First North Premier exchange, which does not have the same legal status as a regulated marketplace. The offering could potentially be the largest on this exchange so far this year. (Dec.)

Investment Banks/Advisors: Avanza Bank AB

ORGENESIS INC.

To meet obligations per terms of its March 2015 acquisition of MasTherCell, Orgenesis Inc. (cell therapies and regenerative medicine) raised $10mm in a financing of equity and debt. In the equity portion, Orgenesis sold accredited investors 8.23mm common shares at $0.52 each (a 58% premium) for gross proceeds of $4.28mm. It also issued three-year warrants to buy the same number of shares at the same price. The company also secured $5mm in debt with two accredited investors. The credit facility terminates on the earlier to occur of November 30, 2016 or when Orgenesis raises in excess of $10mm in an equity investment. As part of the debt financing, the firm issued warrants to buy up to 2.36mm common shares exercisable at $0.53, plus up to 4.72mm in potential three-year drawdown warrants. Orgenesis also announced that since June 2015 it has sold $950k in convertible notes. (Dec.)

RITTER PHARMACEUTICALS INC.

Ritter Pharmaceuticals Inc. (developing therapies for gastrointestinal diseases) sold Aspire Capital Fund $1mm in equity, consisting of 500k common shares at $2.00 each (a 4% discount). Aspire also committed to purchase another $9mm in shares over a 30-month period, during which Ritter controls the timing and amount. (Dec.)

SUNESIS PHARMACEUTICALS INC.

Sunesis Pharmaceuticals Inc. (blood and solid cancer therapies) netted $24mm through concurrent public offerings. The company sold 9.56mm common shares at $8.84 and 20.2k Series B preferred shares at $840 (each share converts into 1k common). Proceeds will go towards upcoming clinical development and regulatory activities. (Dec.)

TEVA PHARMACEUTICAL INDUSTRIES LTD.

Teva Pharmaceuticals Industries Ltd. priced concurrent public offerings of ADSs and convertible preferred shares netting $7.24bn including full exercise of the over-allotment (equivalent amounts raised in each offering). The ADS offering consisted of 59.4mm ADSs at $62.50 (including 5.4mm ADSs through exercise of the over-allotment option) and the convertible preferred offering consisted of 3.7mm shares (including full exercise of the 335.7k over-allotment). The convertible preferred shares will face a mandatory conversion on 12/15/2018 into between 13 1/3 and 16 Adss. These shares will pay a 7% dividend payable quarterly starting on March 15, 2016 on the liquidation preference of $1,000 per share. The proceeds are being used to fund Teva’s already announced acquisition of Allergan’s generic business (previously Actavis) and for it’s Rimsa acquisition. (Dec.)


VIRALYTICS LTD.

Viralysts Ltd. (cancer immunotherapies) raised A$28mm ($20.3mm) through the private sale of 46mm shares at A$0.22 (a 6% discount) to new and existing investors including OrbisMed (which becomes a substantial shareholder), Biotechnology Value Fund, and BVF Partners affiliates. Roth Capital Partners was the placement agent. Proceeds will support the company’s clinical development activities, including a trial collaboration announced in November investigating the combination of Viralytics’ Cavatak with Merck’s Keytruda (pembrolizumab) for late-stage bladder cancer and lung cancer patients. (Dec.)

Investment Banks/Advisors: Roth Capital Partners

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

Mergers & Acquisitions

/Research, Analytical Equipment & Supplies

ADDVISE GROUP AB

LABRUM HOLDING AB

ADDVise Group AB signed a letter of intent to acquire LabRum Holding AB for $4mm (SEK34.5mm) up front plus a potential earn-out of $1.3mm (SEK11.5mm). (Dec.)

The up-front will be paid through a combination of cash, new ADDVise Series B shares, and debt, and the acquisition is expected to close by early 2016. Proforma sales and EBITDA for LabRum (October 2014 - September 2015) are SEK224.3mm and SEK14.7mm, respectively. LabRum is one of Sweden’s largest lab furniture, safety, ventilation and lab equipment companies. The acquisition will result in financial synergies including a higher expected growth rate and will create the largest lab supplier within the Nordic countries. Investment Banks/Advisors: Mangold Fondkommission AB (ADDVise Group AB)

HONEYWELL INTERNATIONAL INC.

SIGMA-ALDRICH CORP.

Honeywell International Inc. acquired the research chemicals business from Sigma-Aldrich Corp. for an undisclosed sum. The acquired business will be folded into Honeywell’s Fine Chemicals business and will retain its core leadership team. (Dec.)

The acquisition includes the Fluka-branded solvents and inorganic chemistry portfolio along with Sigma-Aldrich solvents and the European Economic Area specialty inorganic chemicals. The combined business will reach a broader customer base, expanding into titration products, high-purity solvents, reagents, and specialty inorganic chemicals.
Value-Based Medtech Rides The Money-Go-Round Into 2016
BY ASHLEY YEO
The year 2015 was one of low market growth of just 2% for the wider medtech industry, and companies are facing continued low levels of growth in the established markets for the next three to five years. M&A aside, the best way to win new market share now is by playing to the new payer and provider rules that place a premium on understanding stakeholders’ needs. M&A among medtechs in the $340 billion to $350 billion global market in 2015 is up on 2014 levels, in terms of the sheer amount of mega-deals ($1 billion+) completed during the year. Cardiovascular, patient monitoring and IVD deals (including IVD labs) made up the lion’s share of M&A deals. The industry’s job appears harder – and its operating costs higher – than ever, with 2016 expected to continue throwing new regulatory, reimbursement, market access and technology challenges at what remains the single most innovative industry in terms of the number of patents filed annually.

Pharma’s Love Affair With Dealmaking: No End In Sight
BY PETER CHARLISH
The pace of pharma dealmaking continued unabated in 2015, climaxing with Pfizer’s agreed $160 billion merger with Allergan. Growing shareholder expectations, historically low interest rates, and a new generation of company executives with a financial services background are continuing to drive dealmaking. Pricing continues to be a thorny issue, with more big-ticket launches and even the prices of generics creeping up, although to some extent this may be offset by the appearance of the first biosimilars in the US. Drug pipelines are full and last year also saw a steady flow of innovative new products, notably in the oncology and orphan disease areas.

Diagnostics In 2015: Past Trends Coalesce, New Roads Open
BY MARK RATNER
The introduction of Apple’s ResearchKit is our top story of the year. Mobile apps and the increasing ability to take measurements of vital signs, gather information on habits and collect other phenotypic measures is rapidly changing thinking about clinical trials design. On the dealmaking front, Roche, the market leader in molecular diagnostics, was highly visible. Its most prominent transaction came early; in January, it invested more than $1.16 billion in tumor profiling services organization Foundation Medicine. Roche’s deals attest to two trends heightened in 2015: multiple firms making large bets on liquid biopsy, and increased interest in infectious disease diagnostics.

TG Therapeutics Builds A Business Model For Today
BY MICHAEL GOODMAN
The speed with which TG Therapeutics burst on the scene, along with the potency and safety of its novel combinations of cancer drugs, has perhaps blinded observers to the unique business model that has carried it this far. Its business model is designed to confer multiple benefits across its value chain. It also points the way for small-cap cancer companies in the age of immunoncology: start with proprietary combinations of validated mechanisms, layering on riskier assets over time. TG’s programs – in oncology and in the soon-to-be-christened autoimmune franchise – are largely based on a B-cell depleting backbone combo. If its unprecedented safety profile fades in Phase III trials, the company could be at risk.

Navigating Patent Minefields In Emerging Asian Medtech Markets
BY GABRIELA COMAN
To succeed in Emerging Asian Markets (EAMs), patent applicants need to be aware of current and future business development objectives, market specifics and how local competitors could design around their patented devices. Medtech companies must submit separate patent applications for each country in which they wish to protect their investment and invention. All EAM countries observe a “first-to-file” rule in granting patents, which, in cases where two different entities apply for a patent, the first one to file an application will obtain the patent if the invention is patentable. The US adopted this law in 2013. What is patentable and what is not can be something of a minefield, with different EAMs applying different criteria to patentable matter, so the regulations of each country require very careful scrutiny.