Biopharma boom fosters deal spree

Valuations and volume are up in a buoyant year for biopharmaceutical dealmaking. From tax inversions to gene therapy and, of course, immuno-oncology, 2014 and early 2015 featured plenty of wheeling and dealing.

BY CHRIS MORRISON

Although it was a record year for biopharmaceutical dealmaking—a year that included more than $200 billion worth of mergers and acquisitions—one could argue that the most interesting and dramatic deals of 2014 were the ones that never happened. Those almost-deals, mega-mergers in hot pursuit of corporate-friendly tax climates to drive margin expansion of the combined entities, were eventually thwarted by recalcitrant targets or the slow-to-materialize posturing of the US Treasury. They were massive and oxygen consuming, and their failures set up rebound deals that, though smaller, are no less intriguing.

The failed $117 billion and $53 billion takeovers of AstraZeneca by Pfizer and Shire by AbbVie, respectively, tell only part of the story of 2014's massive dealmaking binge. Those attempted deals, like most of the past few years' larger biopharma deals, were driven and enabled by the previous decade's patent expirations and poor R&D productivity. Currently, however, R&D productivity is seemingly rebounding. A friendlier regulatory climate has taken root, rewarding innovative molecules for unmet needs with speedier-than-ever reviews. Investor enthusiasm for the sector remains at an all-time high, and a renaissance of exciting new technologies and biological understanding may be in the offing. Even with the ever present focus on shareholder returns and deal synergies, more partnerships and buyouts today seem to be driven by the promise of biotech innovation.

That innovation can be sparked by regulatory incentives or by technological advances. Thanks in part to extra marketing exclusivity for qualifying drug candidates, the past 18 months have seen a resurgence of dealmaking in the anti-infectives area, including in the one-time wasteland of antibiotic development. The US priority review voucher program, which lets drug sponsors jump the regulatory queue and may be expanded through the upcoming 21st Century Cures legislation, has increased R&D in pediatric and tropical disease indications alike, and it has sparked a new kind of deal: selling the priority review vouchers themselves.

There have been plenty of bets made on the fruits of experimental platform technologies such as gene therapy and RNA-based therapeutic platforms such as RNAi and antisense RNA, whose times may have finally come. And unsurprisingly, given its evident promise, there is continued enthusiasm for all varieties of cancer immunotherapy, including small- and large-molecule drugs and cellular therapies such as chimeric antigen-receptor T cells (CAR-T) and T cell receptors.

Table 1. Top 10 acquisitions announced in 2014.

Deal	Value
Actavis acquires Allergan	$66 billion
Actavis acquires Forest Laboratories	$22.8 billion
Merck & Co. acquires Cubist Pharmaceuticals	$9.5 billion
Roche acquires Intermune	$8.3 billion
Mallinckrodt acquires Questcor	$5.7 billion
Merck & Co. acquires Idenix	$3.7 billion
Otsuka acquires Avanir	$3.5 billion
Forest Laboratories acquires Aptalis	$2.9 billion
Endo acquires Auxilium	$2.6 billion
Johnson & Johnson acquires Alios	$1.75 billion

Data courtesy of Biocentury's BCIQ Database. All acquisitions are of biopharma companies with patented prescription pharmaceutical focus (excludes devices, diagnostics, OTC, generic-only deals).

BCIQ; Company reports

Among industry's busiest dealmakers are a small handful of newly minted large pharma companies such as Actavis and Valeant Pharmaceuticals, proponents of inorganic growth and dwindling internal R&D spending. These companies join traditional big pharma players hungry for simultaneous growth and therapeutic focus, sharpening competition for bolt-on, revenue-driven acquisitions. At the same time, large biotech companies are using partnership and acquisition strategies to build new growth franchises where one new successful drug could still move the revenue needle. At Celgene, for example, the most talked-about pipeline project is the phase 2 Crohn's disease hopeful GED-0301, an antisense drug program landed in an April 2014 deal for a whopping $710 million up-front payment plus $1.9 billion in potential milestones.

Big pharma's big-game hunts

At the end of the last decade major pharmaceutical companies, impacted by the financial crisis and concerned by the imminent loss of patent exclusivity on blockbuster products, changed their research and development priorities. In particular, a greater proportion of funding was allocated to products in later stages of development. These products are close to commercialization and as such represent a more immediate return on investment. By bringing new products to market, branded pharmaceutical companies aim to offset the $82 billion Datamonitor predicts they will lose due to patent expirations from 2011 to 2014.

In January 2014, Pfizer began its quiet attempts to take over UK-based rival AstraZeneca. In addition to AstraZeneca's UK headquarters, Pfizer had its eye on the company's burgeoning, early-stage immuno-oncology programs and the savings that could mount from a combined commercial and R&D portfolio. The overtures became public when, in April of that year, Pfizer upped its bid in the face of disinterest from the AstraZeneca board. Pfizer's final offer of £69 billion ($117 billion at the time) was rejected in May, and UK law put a damper on further speculation, for a time.

AbbVie initially fared better in its attempt to take over Shire. After an initial $46 billion offer, the companies eventually agreed to a £32 billion ($53.3 billion at the time) deal in June 2014, before the US Treasury, in an attempt to dissuade companies from relocating their headquarters abroad to avoid paying US taxes, announced new policies that would have made the deal prohibitively expensive. The deal was scuttled in October 2014, and Shire walked away the richer, having received a breakup fee of $1.6 billion.

AbbVie's pass at Shire was about more than its tax-friendly location. The big pharma company's need to diversify away from its reliance on its autoimmune powerhouse Humira (adalimumab, the world's best-selling drug, with worldwide sales of more than $12.5 billion in 2014) kept it in the hunt. Eventually, in March 2015, AbbVie swooped in with a $21 billion bid to acquire Imbruvica (ibrutinib) co-marketer Pharmacyclics. The stunning offer apparently trumped those from at least two other suitors, including Pharmacyclics' Imbruvica marketing partner Johnson & Johnson, which only a day earlier reportedly had the deal sewn up. Flush with its breakup bonus, Shire continued to have a busy year that included at least five acquisitions and three alliances, capped by the $5.2 billion takeout of rare-disease specialist NPS Pharmaceuticals in early 2015.

Meanwhile, other big pharma entities entered into asset-swapping agreements that dwarfed most other transactions. GlaxoSmithKline sent

its marketed oncology portfolio to Novartis for $16 billion and paid $7.2 billion for Novartis's vaccine portfolio in return. Bayer Healthcare paid more than $14 billion for Merck's consumer healthcare business less than 2 weeks later (concurrently the companies signed a co-development and co-commercialization deal around Bayer's guanylate cyclase modulators that called for a $1 billion up-front payment from Merck). Those deals, at least on the surface, are examples of the industry's largest companies embracing some measure of portfolio focus.

Other deals were driven by attempts to bolster cost savings. Valeant tried to corner Allergan, the maker of Botox (onabotulinumtoxinA), with a series of hostile overtures: an initial bid of $45 billion in cash and stock was raised twice, to $53 billion, before white-knight acquirer Actavis stepped in with a friendly $65 billion offer in November 2014. (That deal, combined with Actavis's February 2014 acquisition of Forest Laboratories for $23.9 billion and the relatively modest $675 million it paid up front for antibiotic specialist Durata Therapeutics in November, made the erstwhile generic specialist the year's biggest spender by far, during a period that completely transformed the company (**Table 1**).)

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>
> **IAN READ, CEO OF PFIZER**

Splurging on immuno-oncology

Like AbbVie, Pfizer saw more than a tax shelter in its corporate quarry. AstraZeneca had experienced a woeful few years of patent expiries and an R&D slump, but new senior management had repositioned the company for growth. CEO Pascal Soriot, in making the case to analysts for an independent AstraZeneca (or at least a better bid from Pfizer) in May 2014, outlined a pipeline with (non-risk-adjusted) peak sales of $63 billion. The pipeline jewel was the immuno-oncology drug candidate MEDI4736, a phase 2/3 antibody to PD-L1.

Pfizer had to turn elsewhere. At $850 million up front for a phase 1 asset, its November 2014 deal for avelumab with Merck KGAA's Merck Serono pharmaceutical division might seem expensive, but that asset—like MEDI4736—could become a cornerstone of both companies' immuno-oncology franchises, just as immuno-oncology is becoming an industry-wide cornerstone of future revenue and relevance.

Pfizer chairman and CEO Ian Read has steadfastly defended the deal, which includes regulatory and commercial milestone payments of up to $2 billion and will allow Merck Serono to co-promote Pfizer's kinase inhibitor Xalkori (crizotinib) in the United States and other "key markets." Read told the audience during a fireside chat at the February 2015 BIO CEO & Investor meeting, in New York, that some Pfizer observers thought the company overpaid to access avelumab. But, he argued, "the market doesn't see that the value [of cancer immunotherapies] isn't in the first wave, the value is in the combination products that are going to follow."

It is the hunt for these combinations that has driven a healthy portion of biopharma companies' dealmaking strategies over the past 2 years to either build—as companies such as Roche and Bristol-Myers Squibb are wont to do—an "all under one roof" immunotherapy solution or partner with peers to pair up candidates from among the alphanumeric soup of targeted agents (IDOs, CTLA-4s, PD-1s, CDK4/6s, PD-L1s, OX40s and many more) in clinical trials. That dealmaking has taken place against the backdrop of an unprecedented biopharma bull market, one that has seen soaring valuations—fueled, of course, by the very prospect of large deals—and more than 100 newly public biotech companies raising well over $10 billion in aggregate initial public offerings and follow-ons. In short, and particularly in the immuno-oncology space, it's a seller's market, and although it is perched at the top of the charts, $850 million up front for a phase 1 oncology drug candidate isn't the outlier it might initially seem to be.

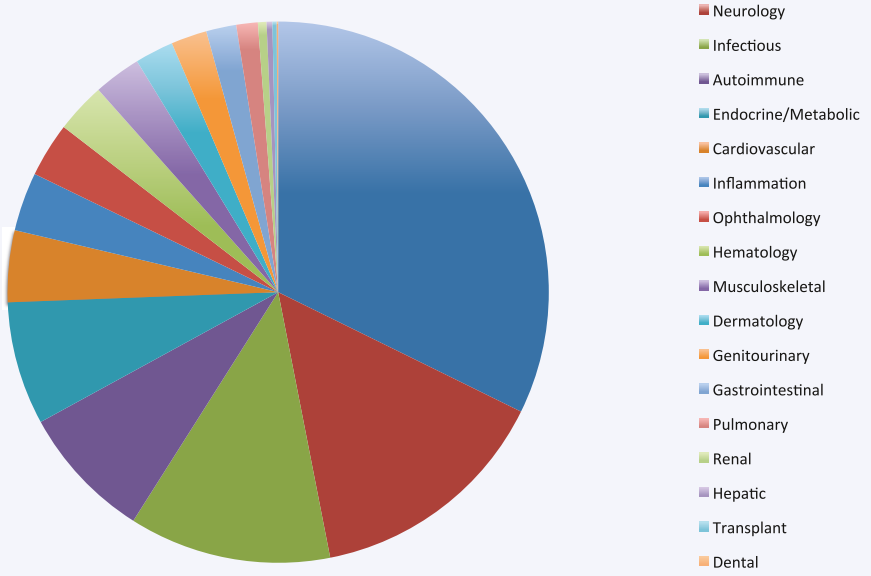
Take, for example, the $800 million up front that Bristol-Myers Squibb paid in February 2015 to acquire Flexus Biosciences ($450 million in development milestones could take the near-term value of that deal to $1.25 billion). Flexus's lead candidate, the preclinical small-molecule IDO1 inhibitor F001287, is Bristol's only real prize; besides F001287, the deal netted the big pharma company some related discovery programs. The rest of Flexus's non-IDO-related assets (including clinical-stage candidates) will remain with Flexus's venture backers, essentially making what's ostensibly an acquisition better resemble an upfront-loaded licensing deal. The company was founded only recently, in 2013, and had raised $38 million from Kleiner Perkins Caufield and Byers, the Column Group and Celgene.

The Flexus compound may someday take a place beside—or potentially in combination with—Bristol-Myers Squibb's blockbusters Yervoy (ipilimumab), a CTLA-4 inhibitor, and Opdivo (nivolumab), a PD-1 inhibitor, both immuno-oncology trailblazers currently approved for certain skin and lung cancer indications. The big pharma company has entered into several other immuno-oncology deals over the past several months, including deals with Rigel Pharmaceuticals ($30 million up front for a TGF-β inhibitor), Bavarian Nordic ($60 million up front for Prostvac, a cancer vaccine) and Five Prime Therapeutics ($30 million up front for an antibody to CSF1R), to name a few.

Shopping CAR-T

The deal scene in immuno-oncology extends beyond small-molecule- and antibody-based approaches to tackling cancer and into the exciting field of cell therapy. Novartis was the first big biopharma company to enter the space, through its alliance with the University of Pennsylvania, in 2012. But as academic-center technology has been transferred to biotech companies—Kite Pharma, Juno Therapeutics, Cellectis, Bellicum and Adaptimmune have all either gone public or announced plans to do so in the past 2 years—so have the deals.

In January 2015, Amgen teamed up with Kite Pharma, pairing Kite's cell-therapy technology with Amgen's expertise in cancer-target biology in an alliance that could see either company earning $525 million in milestones on projects developed by its partner, plus royalties. Kite also received $60 million up front, and Amgen will pay expenses through investigational new drug (IND) filing. That deal followed Pfizer's initial foray into CAR-T, a June 2014 alliance with French biotech company Cellectis. Cellectis received $80 million up front and R&D funding, and it is eligible for an additional $185 million in milestone payments, plus future royalties. That same month, GlaxoSmithKline also entered the fray, through a deal with UK-US biotech company Adaptimmune in the related field of engineered T cell receptors. That deal included co-development of Adaptimmune's lead program for NY-ESO-1 and an option to license the phase 1 program at proof of concept. The companies estimated that the deal could be worth more than $350 million to Adaptimmune over the next 7 years, plus royalties.



BCIQ; Company reports

Figure 1: Number of partnering deals by therapeutic area (2013–Q1/2015).

Incentivizing antibiotics and a price tag on priority

Anti-infectives in general have been attractive business-development targets. According to BioCentury's records on deals related to pharmaceutical products, discovery and targets, only the areas of cancer and neurology have featured more deals since 2013 (cancer, predictably, had more than twice as many deals as neurology, the second-place category) (**Fig. 1**).

The infectious-disease partnerships included five focused on Ebola virus, sparked by the Ebola outbreak in Africa and global public health concerns over a potential pandemic. Merck, for example, paid $30 million up front for exclusive rights to a phase 1 Ebola vaccine from NewLink Genetics. In addition, worry over the lack of novel antibiotics and increasing bacterial resistance to the existing arsenal has spurred legislators to create incentives that will attract drug makers back to the field. Those incentives—such as the extra patent exclusivity assigned to Qualified Infectious Disease Pathogen treatments under the 2012 Generating Antibiotic Incentives Now (GAIN) Act—may be driving R&D and business-development investments.

Most notable was Merck's $9.5 billion acquisition of Cubist Pharmaceuticals in December 2014 (Cubist itself had bought Trius Therapeutics and Optimer Pharmaceuticals, for $707 million and $535 million, respectively, in July 2013). That deal was done at a 35% premium relative to the value of Cubist's shares over the previous five trading days. Had Merck waited another day, it might have come cheaper: on the day the deal was announced, a federal judge invalidated several patents on Cubist's blockbuster Cubicin (daptomycin), effectively accelerating generic competition by a few years. Still, Merck's presence in the antibiotics marketplace was seen by some as a sign that incentives are working as intended.

Another legislative success story that had interesting implications for dealmaking in 2014 was the priority review voucher (PRV) program. In August 2014, Sanofi and Regeneron Pharmaceuticals paid $67.5 million to BioMarin Pharmaceuticals to obtain BioMarin's PRV (BioMarin was granted the voucher earlier in the year when its Vimizim (elosulfase alfa) received FDA approval for treatment of the rare pediatric disease Morquio A syndrome). Sanofi and Regeneron then used their PRV to gain valuable time in the race with Amgen to get the first PCSK9 cholesterol-lowering drug to market; once a few months behind, Sanofi and Regeneron are now neck-and-neck with their rival. And the price for PRVs appears to be rising: in November 2014, Gilead Sciences paid Knight Therapeutics $125 million for the PRV Knight received when the leishmaniasis treatment Impavido (miltefosine) got an FDA nod earlier in 2014. Gilead has yet to decide where to put its PRV to work.

RNA rising

CAR-T therapy is just one example of the types of approaches rejuvenating the pharma industry's interest in new therapeutic modalities. Gene therapies have also enjoyed the attention of large companies' business-development teams (see *Curative therapeutics take the stage*, **page B35**). Since June 2014, three gene-therapy deals have been signed in the hemophilia space alone: Bayer Healthcare teamed up with Dimension Therapeutics in June 2014 to fund Dimension's preclinical hemophilia A program,

Table 2. Select RNAi therapeutics deals (2014-2015).

Date	Companies/Deal Type	Terms
January 2014	Sanofi's **Genzyme** broadened RNAi alliance with **Alnylam**	The companies expanded a 2012 alliance under terms that provided Genzyme with a a 12% stake in Alnylam, valued at $700 million. Genzyme will get exclusive worldwide options on Alnylam pipeline outside of US and Western Europe.
January 2014	**Moderna** granted **Alexion** exclusive options to license rights to develop and commercialize compounds discovered and manufactured by Moderna using its mRNA platform against undisclosed targets selected by Alexion for rare disease	Moderna will receive $100 million up front and is also eligible for undisclosed milestones, plus high single-digit to double-digit royalties. Alexion also made a $25 million equity investment in Moderna.
April 2014	**InDex** granted **Almirall** rights to develop and commercialize Kappaproct in Europe to treat ulcerative colitis	InDex is eligible for up €20 million ($27.5 million) in upfront and "near term" milestone payments and up to €80 million ($110.1 million) in regulatory and sales milestones, plus double-digit royalties.
August 2014	**Roche** acquires partner **Santaris** for locked-nucleic-acid platform and pipeline	Santaris investors will receive $250 million up-front plus $200 million in earn-out payments.
January 2015	**Merck** and **Moderna** partnered to discover, develop and commercialize five mRNA-based treatments and vaccines against four undisclosed viruses	Merck will make an upfront cash payment to Moderna of $50 million and a $50 million equity investment in Moderna. Moderna will also be eligible for undisclosed per-product development and commercial milestones, as well as tiered royalties on sales.

Data courtesy of Biocentury's BCIQ Data.

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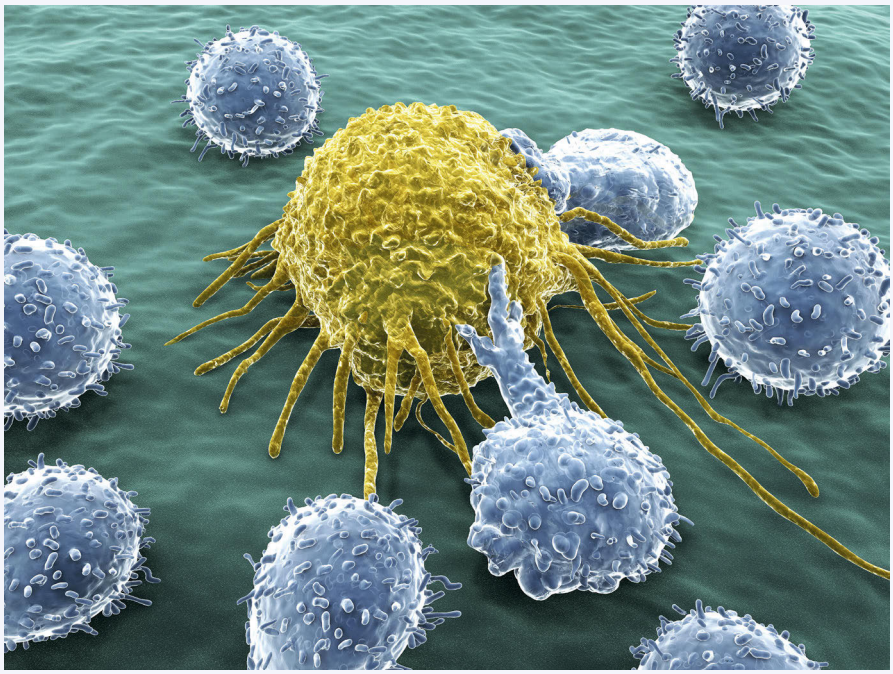

Figure 2: Cancerous cell and lymphocytes. Success in the clinic bolstered interest in companies developing immune system modulators for treating cancer.

Pfizer inked a deal with Spark Therapeutics in December 2014 around Spark's hemophilia B therapy, and in January 2015 Biogen partnered with the Italian San Raffaele Telethon Institute for Gene Therapy to develop gene therapies for hemophilia A and B.

Most recently, in early April 2015, Bristol-Myers Squibb and Uniqure—a Dutch biotech company with the only gene therapy approved in a major market—said they would work together to develop gene therapies for cardiovascular disease and possibly other indications. That deal includes near-term payments to Uniqure of about $100 million (which includes an equity component of about $32 million). The deal encompasses up to ten targets, including Uniqure's lead program in congestive heart failure. So far, the biggest gene-therapy deal of the past few years is one struck in February 2015, in which Sanofi's Genzyme division paid $100 million up front to Voyager Therapeutics to establish a strategic alliance around therapies for severe central nervous system disorders that could eventually net Voyager up to $845 million (see *Curative therapeutics take the stage*, **page B35**).

Genzyme also upped its participation in RNAi, through an expanded deal with Alnylam in January 2014. The broadened alliance included a $700 million equity investment in Alnylam (a 12% stake, for which Genzyme paid a 25% premium over the market price) for an exclusive option for non–North American and Western European rights to what is essentially Alnylam's entire near-term pipeline of RNAi candidates for genetically defined diseases. Other highlights in RNA therapies included Roche's $450 million ($250 million up front) acquisition of partner Santaris in August 2014, for its pipeline of programs in locked nucleic acids. And Moderna Therapeutics, the messenger RNA therapeutics specialist, added to its stable of partners with two deals: in January 2014 it partnered with Alexion Pharmaceuticals ($125 million up front, including a $25 million equity stake) in rare diseases, and in January 2015 it partnered with Merck & Co. ($100 million up front, including a $50 million equity stake) in viral diseases (**Table 2**).

Valuations rising

For now this biotech seller's market continues unabated, but biotech valuations may soon reach a point that puts a damper on dealmaking. Merck, analysts argued, paid too much for Cubist, only months after the company supposedly paid too much ($3.7 billion) to buy hepatitis C–focused Idenix Pharmaceuticals. Similarly, investors and analysts felt AbbVie paid too much to acquire Pharmacyclics; $21 billion for partial rights to a blockbuster certainly set a new high-water mark.

And it's not just in the multibillion-dollar acquisitions that valuation creep is pushing deal premiums ever higher. In 2013, the average 30-d premium on acquisitions sat at an impressive 45.7%, according to an analysis of BioCentury data. In 2014, that figure rose to 54.3%, and for the first quarter of 2015 it was 56.4% (though based on limited data).

Acquisitions of privately held venture-backed biotech companies have risen as well. According to data from Informa's Strategic Transactions database, the average multiple (the price paid divided by how much a company raised from venture investors) commanded in these deals spiked in 2014, increasing by more than five times on the basis of up-front payments only and more than eight times when all earn-outs are included.

Of course, in 2011, Gilead's $11 billion buyout of sofosbuvir developer Pharmasset—a record for an acquisition of a phase 2 asset—seemed mighty expensive as well. That drug, now marketed as the hepatitis C virus polymerase inhibitor Sovaldi, and a key component of Sovaldi successor Harvoni, has enjoyed the best pharmaceutical launch of all time. In 2014, Sovaldi posted revenues of more than $10 billion, and it is poised to overtake Humira as the world's most lucrative drug. When it comes to valuation, only time will tell.

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