

White Paper

# IMS PharmaDeals

## Review of 2015

Return of the mega-merger and a shift to early-stage dealmaking

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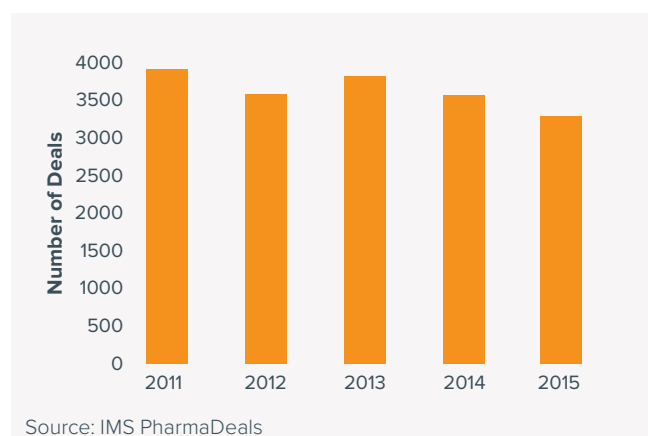
The strong M&A activity that emerged in 2014 was maintained in 2015, driven by the pursuit of growth and the availability of cheap debt finance. Pharmaceutical companies continued to offload non-core assets and were willing to pay sizeable premiums to acquire key late-stage programmes, while consolidation in the generics sector persisted. On average, licensing upfront payments and deal values fell in 2015 relative to 2014, although they still remained robust. For the third year running, AstraZeneca was the most prolific dealmaker, this time by some margin, although Pfizer topped the rankings in terms of deal spend. Oncology, and the field of immuno-oncology in particular, continued to dominate the dealmaking landscape, although there was some noteworthy early-stage deal activity for novel biological programmes across a variety of therapy areas.

## Strong appetite for M&A remains

Deal activity in the life sciences sector has been in decline in recent years. A review of the IMS PharmaDeals database of publicly disclosed deal activity reveals that the number of agreements signed, not including standalone research grants, decreased by approximately 10% from 2014 to 2015 (Figure 1). Indeed, after peaking in 2011, deal activity is now at its lowest level for 5 years. There are a number of factors contributing to this downturn, including industry consolidation, the focused dealmaking strategies being pursued by many pharmaceutical companies and the unparalleled availability of funding for early-stage biotechs, meaning that partnering deals no longer represent the only realistically accessible source of capital for such companies. While the IPO window remained open in 2015, the second half of the year saw a dwindling number of discounted offerings. Market turbulence and concerns over drug pricing and valuations also prompted the Nasdaq Biotechnology Index to fall 15% after reaching its peak in July<sup>1</sup>.

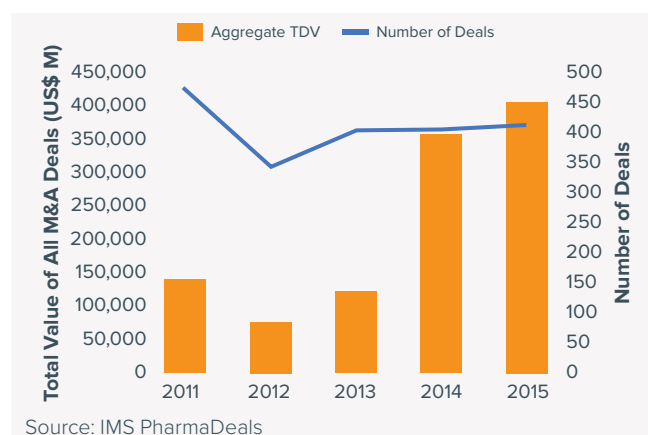
Despite the overall downturn in deal activity, the volume of M&A deals (defined here as Mergers, Business Acquisitions and Divestments, signed but not necessarily completed) actually increased slightly from 2014 to 2015 (Figure 2). Following on from what was an unprecedented year for

**Figure 1: Number of deals (excluding funding awards), 2011-2015.**

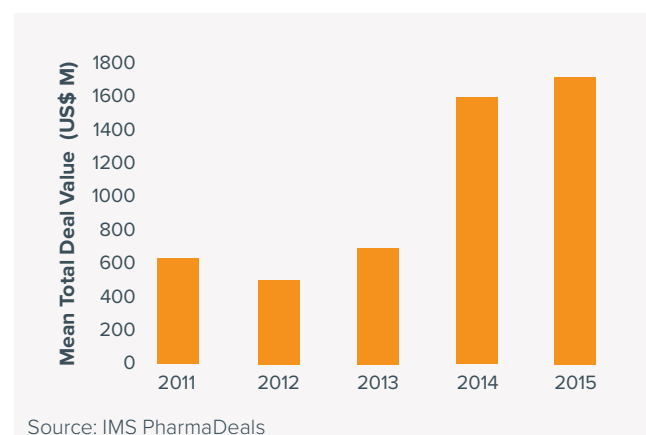


industry consolidation, big pharma appetite for M&A remained robust in 2015, a year that saw the return of the mega-merger. At US\$402.8 B, the aggregate total value of all M&A deals signed in 2015 was 15% higher than the equivalent figure for 2014 and far in excess of the combined total value of M&A deals in any year since the IMS PharmaDeals database began collecting and indexing deals in May 1996 (Table 1). Furthermore, the mean total deal value for M&A deals increased 7% from US\$1594 M in 2014 to US\$1707 M in 2015 (Figure 3), although the median total deal value actually fell 10% to US\$127.5 M in 2015 (Table 1).

**Figure 2: Number and aggregate total value of M&A deals, 2011-2015.**



**Figure 3: Mean total deal value of M&A deals, 2011-2015.**



<sup>1</sup> Yahoo Finance

**Table 1: Aggregate, mean and median values of M&A deals, 2014 vs. 2015.**

	2014	2015	Change
Aggregate value of all M&A deals	US\$350,641 M	US\$402,838 M	+15%
Mean deal value	US\$1594 M	US\$1707 M	+7%
Median deal value	US\$141.7 M	US\$127.5 M	-10%

Source: IMS PharmaDeals

There are a number of factors contributing to this level of M&A activity, including healthy balance sheets and the ready availability of cheap debt financing, the strategic need for companies to refuel pipelines and drive future growth, as well as fierce competition for desirable assets driving up valuations and in some cases sparking bidding wars.

The M&A headlines in 2015 were dominated by Pfizer's US\$160 B mega-merger with Irish domiciled Allergan (Deal no. 68062), which is by far the largest deal in the history of the pharmaceutical industry, eclipsing Pfizer's own US\$90 B takeover of Warner-Lambert in 2000 (Deal no. 5536). In order to bypass US Treasury tax inversion rules, which state that the original shareholders of the non-US company must own at least 40% of the combined entity, the deal has been structured as a reverse merger so that the smaller Allergan is technically acquiring the much larger Pfizer. Assuming that the maximum cash component of US\$12 B is paid in the merger, it is expected that former Pfizer shareholders will own approximately 56% of the combined company, while Allergan shareholders will own approximately 44%.

As well as significant tax benefits owing to Allergan's Irish tax domicile, the deal offers Pfizer diversification into new therapy areas thanks to products such as Botox® (onabotulinumtoxinA) and Restasis® (cyclosporine ophthalmic emulsion), the prospect of double-digit branded sales growth and a pipeline strengthened with the addition of 70 mid- to late-stage development opportunities. Moreover, as Allergan currently generates 85% of its business in North America, significant opportunity exists to drive revenue growth outside this market by utilising Pfizer's global commercial infrastructure. Unsurprisingly, Pfizer was by far the largest spender on M&A in 2015, with its US\$17 B purchase of generic injectables specialist Hospira (Deal no. 63279) bringing its total M&A spend for the year to a staggering US\$177 B.

Combined, the top 10 M&A deals of 2015, as ranked by total potential deal value and recorded in the IMS PharmaDeals database, had an aggregate value of US\$298.30 B, a figure 31% higher than the combined value of the top 10 M&A deals of 2014 in major part due to the magnitude of the Pfizer/Allergan deal (Table 2). Interestingly, while eight of the top 10 deals of 2014 had a deal value in excess of US\$10 B, there were only six US\$10 B-plus deals signed in 2015. Nevertheless, 41 M&A deals in 2015 had a value of between US\$1 B and US\$10 B, compared to 29 in 2014, indicative of buoyant market valuations.

**Table 2: Top M&A deals of 2015 ranked by total deal value.**

Total Deal Value	Companies	Deal Driver
US\$160 B	Pfizer, Allergan	Tax benefits, revenue growth, therapy area diversification
US\$40.5 B	Teva, Allergan Generics	Increased scale and pricing power in the generics market
US\$21 B	AbbVie, Pharmacyclics	Imbruvica® (ibrutinib), a Bruton's tyrosine kinase inhibitor approved for the treatment of certain B-cell malignancies
US\$17 B	Pfizer, Hospira	Portfolio of marketed generic injectables
US\$15.8 B	Valeant Pharmaceuticals International, Salix Pharmaceuticals	Portfolio of marketed gastrointestinal drugs
US\$13.8 B	Danaher, Pall	Filtration, purification and separation business
US\$8.4 B	Alexion Pharmaceuticals, Synageva BioPharma	Kanuma™ (sebelipase alpha), an enzyme replacement therapy for lysosomal acid lipase deficiency
US\$8.05 B	Endo International, Par Pharmaceutical	High-barrier-to-entry generic drugs and branded speciality pharmaceuticals
US\$7.2 B	Celgene, Receptos	Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator in Phase III for relapsing multiple sclerosis and ulcerative colitis
US\$6.546 B	Shire, Dyax	DX-2930, a Phase III-ready plasma kallikrein inhibitor for the prevention of type 1 and type 2 hereditary angioedema

Source: IMS PharmaDeals

After a period of cost-cutting and restructuring, Teva returned to M&A in 2015, beginning with the US\$3.5 B purchase of Auspex Pharmaceuticals and its portfolio of drug candidates for hyperkinetic movement disorders (Deal no. 64135). Appeasing analysts who had been hoping for a significantly larger purchase, the company subsequently instigated a US\$40 B hostile approach for rival Mylan but later dropped this in favour of a US\$40.5 B cash and stock deal to buy Allergan's global generics business, by far the largest in its history (Deal no. 65784). With the acquisition, Teva will consolidate its position as the leading global generics player ahead of Sandoz and Mylan, with a market share in excess of 20%. The deal will also add more than 1000 products to Teva's existing US\$9.1 B generics business, enable it to realise cost synergies and tax savings of approximately US\$1.4 B annually and increase the company's leverage in negotiating drug prices with private healthcare insurers and other payers, something which is particularly important in the US market where Teva has seen the market share of its top 3 customers increase significantly in recent years as a result of channel consolidation.



Later in the year, Teva went on to purchase a 51% equity stake in genomic analysis company Immuneering (Deal no. 65859), acquire Gecko Health Innovations and its cloud-based solution for chronic respiratory disease management (Deal no. 66941) and agree to acquire the Mexican pharmaceutical company Representaciones e Investigaciones Médicas (Rimsa) for an aggregate consideration of US\$2300 M (Deal no. 66969).

Four of the top 10 M&A deals of 2015 were driven by single assets and the pursuit of diversification. AbbVie's US\$21 B acquisition of Pharmacyclics, the largest deal to be announced in H1 2015, was all about the potential multibillion dollar blockbuster Imbruvica® (ibrutinib), a Bruton's tyrosine kinase (Btk) inhibitor that is approved in the US and Europe for the treatment of a number of B-cell malignancies and which AbbVie hopes will help diversify its business beyond Humira® (adalimumab) (Deal no. 63745). The purchase price shocked many industry observers, however, effectively valuing Imbruvica at a staggering US\$42 B given Janssen Biotech's 50% interest in the drug (Deal no. 44377). With its US\$8.4 B cash-and-stock purchase of Synageva BioPharma, Alexion Pharmaceuticals gained Kanuma™ (sebelipase alpha), an enzyme replacement therapy for lysosomal acid lipase deficiency that was approved by the US FDA in December 2015 (Deal no. 64607), while Celgene's purchase of Receptos (Deal no. 65530) and Shire's takeover of Dyax (Deal no. 67649) were also driven by single late-stage assets, namely the oral sphingosine 1-phosphate (S1P) receptor modulator ozanimod and the plasma kallikrein inhibitor DX-2930, respectively.

Big pharma asset disposals, which were a key M&A theme of 2014, continued unabated in 2015 as companies focused their product portfolios further and disposed of non-core offerings. GlaxoSmithKline (GSK), for example, sold its quadrivalent meningitis ACWY vaccines, Nimenrix® and Mencevax®, to Pfizer for US\$130 M (Deal no. 65213), a portfolio of OTC brands to Perrigo for €200 M (US\$226 M) (Deal no. 64964) and divested its rights in ofatumumab for autoimmune indications, including multiple sclerosis, to Novartis for up to US\$1034 M plus up to 12% royalties (Deal no. 66146). Astellas Pharma agreed to transfer its global dermatology business to LEO Pharma for €675 M (US\$724 M) (Deal no. 67764), AstraZeneca acquired the rights to Actavis' (Allergan's) branded respiratory business in the US and Canada for an initial consideration of US\$600 M (Deal no. 63274) and Bristol-Myers Squibb (BMS) sold its entire HIV pipeline to ViiV Healthcare via two separate deals together worth almost US\$3 B (Deal no. 68559).

## AstraZeneca extends its dealmaking lead

For the third year running, AstraZeneca has retained its title as the most prolific pharmaceutical dealmaker with 78 publicly disclosed deals, a notable step up from the previous year (Figure 4). Following behind in the deal activity rankings are Johnson & Johnson (J&J) and Roche with 62 and 49 deals, respectively, a slight decrease for both companies on 2014. AstraZeneca's high level of deal activity forms part of a strategy to nearly double the company's sales to US\$45 B by 2023 and 2015 saw the company invest heavily in rebuilding its pipeline as it looks for new sources of revenue to replace Nexium® (esomeprazole) and Crestor® (rosuvastatin). The company's largest deal of the year was its acquisition of a 55% stake in Acerta Pharma for an upfront payment of US\$2.5 B plus a further unconditional payment of US\$1.5 B (Deal no. 68542). The key driver of the deal was Acerta's acalabrutinib, an irreversible oral Btk inhibitor in Phase III development for B-cell blood cancers and in Phase I/II clinical trials in multiple solid tumours and a potential competitor to Imbruvica. As part of the deal, AstraZeneca has the option to buy the rest of the company.

In order to boost the long-term prospects of its declining cardiovascular and metabolic diseases franchise, in November AstraZeneca outbid Actelion with a US\$2.7 B all-cash deal to acquire ZS Pharma (Deal no. 67729). The deal gives AstraZeneca full rights to ZS Pharma's lead asset ZS-9 (sodium zirconium cyclosilicate), a highly selective potassium binder for the treatment of hyperkalaemia that is awaiting a regulatory decision from the FDA. Cardiovascular and metabolic diseases represent a therapeutic area of focus for AstraZeneca and the acquisition of ZS-9 will help strengthen the company's pipeline in this area, which is somewhat lacking in late-stage assets

Figure 4: Most prolific dealmakers, 2014 vs. 2015.



and includes roxadustat, an inhibitor of hypoxia-inducible factor (HIF) prolyl hydroxylase that is currently in Phase III development for patients with anaemia associated with chronic kidney disease and which is partnered with FibroGen (Deal no. 53779). The uptake of ZS-9, however, will depend on whether the drug is able to demonstrate a differentiated safety profile relative to Relypsa's Veltassa™ (patiomer calcium), which became the first new treatment for hyperkalaemia in more than 50 years when it was approved by the FDA in October 2015.

In an attempt to boost its earnings in the near term, AstraZeneca also furthered its externalisation strategy in 2015, receiving US\$200 M upfront from Daiichi Sankyo in return for US co-commercialisation rights to its opioid-induced constipation therapy Movantik™ (naloxegol) (Deal no. 63995). It later out-licensed its immune checkpoint inhibitor MEDI4736 (durvalumab) to Celgene for development in haematological malignancies in return for US\$450 M upfront (Deal no. 64454), licensed brodalumab to Valeant Pharmaceuticals International for US\$100 M upfront (Deal no. 66380), divested Caprelsa® (vandetanib) to Sanofi's Genzyme unit for up to US\$300 M (Deal no. 65743) and sold US rights to Entocort® (budesonide) to Perrigo for US\$380 M (Deal no. 68043) and ex-US rights to the same drug to Tillotts Pharma for US\$250 M (Deal no. 65472).

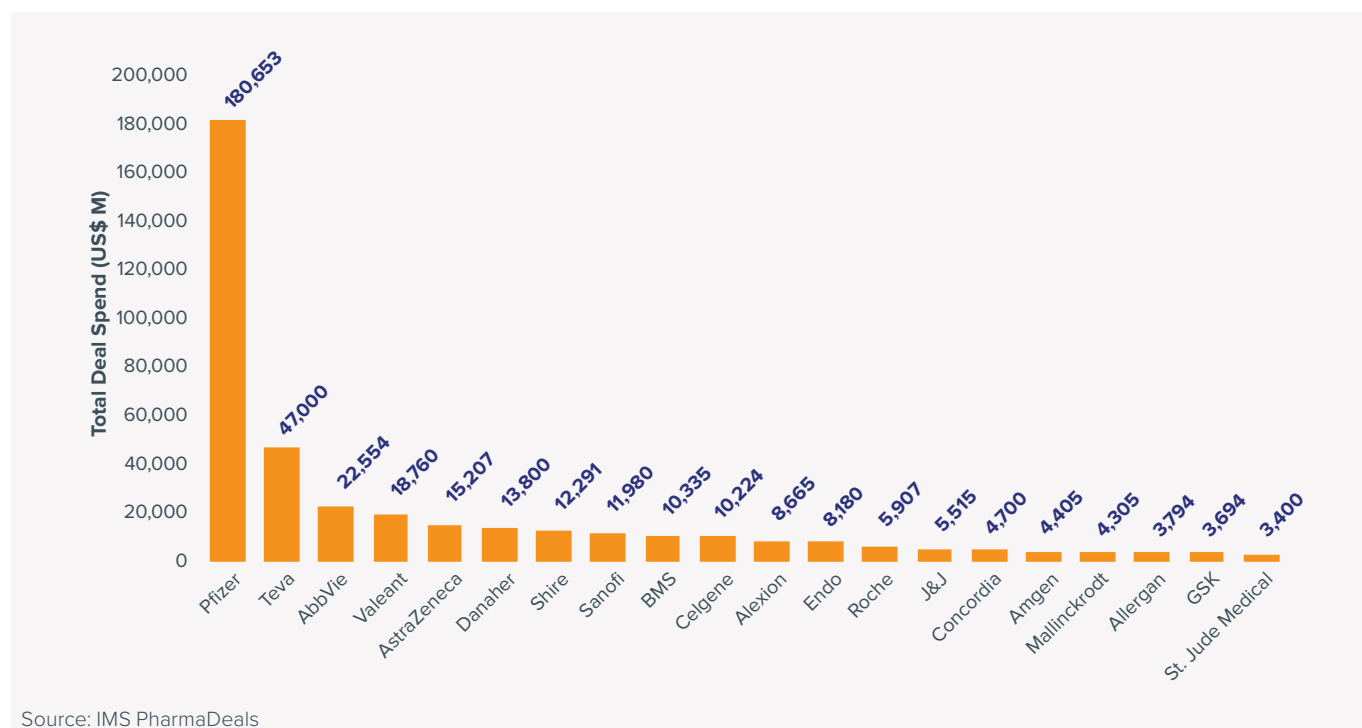
Intent on reclaiming market share lost to Gilead Sciences' Harvoni® (ledipasvir + sofosbuvir), in May J&J's Janssen Pharmaceuticals licensed worldwide development and commercialisation rights to Achillion Pharmaceuticals' lead hepatitis C virus (HCV) assets, including its Phase II second-generation NS5A inhibitor ACH-3102, with the aim of developing an oral treatment regimen that could work in as little as 6 weeks (Deal no. 64761). The deal, the company's largest of the year in terms of headline value, is notable for the absence of an upfront payment, with J&J's venture capital arm instead making a US\$225 M equity investment in the HCV drug developer. Otherwise, J&J's deals were very much biased towards the early stages of development. In November, for example, and in exchange for US\$105 M upfront the company's Janssen division licensed worldwide rights, excluding China and Korea, to Hanmi Pharmaceuticals' oxyntomodulin-based therapies including HM12525A, a biologic that is completing Phase I and which is expected to enter Phase II studies in 2016 (Deal no. 67761).

Roche continued to exhibit a preference for bolt-on acquisitions in 2015, acquiring Adheron Therapeutics and its technology platform that disrupts cell adhesion (Deal no. 67128), French biotech Trophos and its Phase III asset for spinal muscular atrophy (Deal no. 63015), microbiology diagnostics company GeneWEAVE BioSciences (Deal no. 66013), liquid biopsy start-up CAPP Medical (Deal no. 64289), Signature Diagnostics (Deal no. 63344) and genomic tools provider Kapa Biosystems (Deal no. 66135). The company also spent US\$1.03 B to acquire a majority stake in Foundation Medicine as part of a deal that includes a broad R&D collaboration in the field of molecular information in oncology (Deal no. 63048).

Figure 5 presents an analysis of the leading companies as ranked by the aggregate total deal value of each company's deals in 2015, excluding those deals where the company is itself receiving payment e.g. out-licensing agreements or divestments. As licensing and collaborative deals are included in the analysis, the total deal spend may not be realised in many cases. Each of these 20 companies pledged to spend more than US\$3 B on deals in 2015. Although its deal activity in terms of deal volume fell in 2015 as it focused its attention on M&A, Pfizer tops the deal spend rankings by a considerable margin.



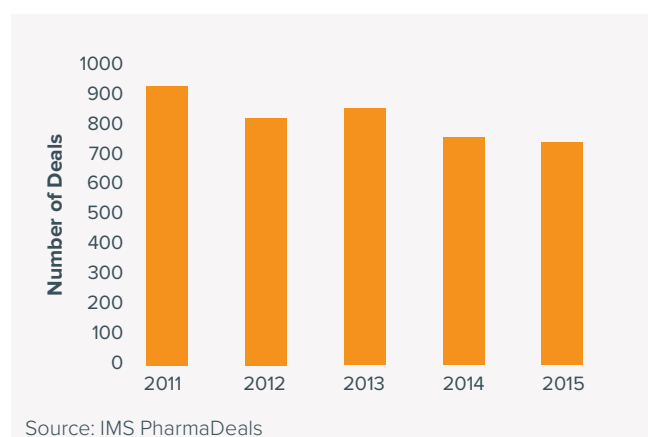
**Figure 5: Top 20 companies ranked by aggregate total value of all disclosed deals in 2015 (excluding out-licensing deals and divestments by such companies).**



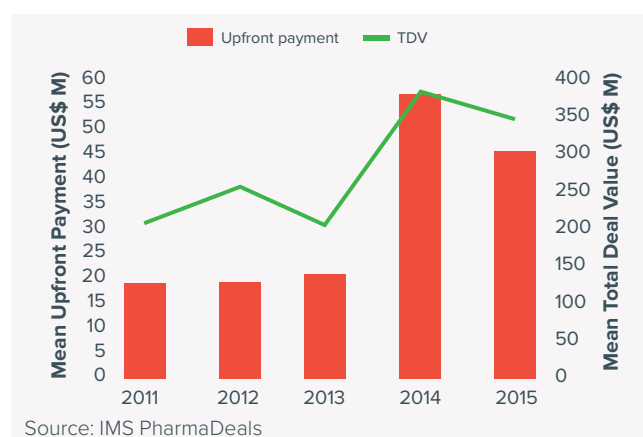
## Licensing activity remains robust but fails to reach 2014 levels

Licensing activity in the life sciences sector, which peaked in 2011, fell by 3% from 2014 to 2015, a less pronounced drop than from 2013 to 2014 (Figure 6). However, the mean total deal value, excluding royalties, for licensing deals with disclosed financial information fell 10% from 2014 to 2015 to reach US\$342 M, while the mean cash upfront payment for these deals fell 20% to US\$45.1 M (Figure 7).

**Figure 6: Number of licensing deals, 2011-2015.**



**Figure 7: Mean total deal value and mean upfront payment for licensing deals, 2011-2015.**



This is in part due to the absence of licensing deal terms of the unprecedented magnitude seen in 2014, such as the US\$1000 M upfront that Merck & Co. paid Bayer as part of a US\$2100 M global collaboration between the parties to develop and market Bayer's portfolio of soluble guanylate cyclase modulators for cardiovascular diseases led by Adempas® (riociguat) (Deal no. 58596). Nevertheless, the mean upfront payment and mean total deal value for licensing deals recorded in the IMS PharmaDeals database were still significantly higher in 2015 than for any year in the 2011–2013 time period.

The highest upfront payments in 2015 were reserved for clinical-stage assets in the immuno-oncology, inflammatory disease and diabetes therapy areas. Table 3 presents the top 10 partnering deals of 2015 as ranked by upfront consideration (including both cash and equity investments). Significantly, all of these deals have an upfront consideration in excess of US\$250 M, whereas this was the case for only the top 5 partnering deals of 2014. The largest total upfront payment was the jaw-dropping US\$1 B in cash and equity that Celgene agreed to pay in order to access Juno Therapeutics' pipeline of chimeric antigen receptor technology (CAR-T) and T-cell receptor (TCR) programmes over a 10-year period, although the cash component was only US\$150 M (Deal no. 65423). The second ranked deal, Gilead's partnership with Galapagos for the Phase III-ready JAK1 (Janus kinase 1) inhibitor filgotinib, also includes a significant equity component alongside a sizeable cash payment (Deal no. 68579). This deal is notable, coming as it does less than 3 months after AbbVie terminated its 2012 agreement with Galapagos for the development and commercialisation of filgotinib and instead decided to move forward with the development of its own JAK1 inhibitor ABT-494, which entered Phase III trials for rheumatoid arthritis in December 2015 (Deal no. 45670).

Interestingly, Sanofi appears in the top partnering deals list three times, thanks to its agreements with Regeneron Pharmaceuticals (Deal no. 65799), Hanmi Pharmaceutical (Deal no. 67687) and Lexicon Pharmaceuticals (Deal no. 67725). The latter two deals are in the diabetes field, concern clinical-stage assets and are aimed at safeguarding the long-term prospects of the company's franchise in this disease area. Diabetes has been a key growth platform for Sanofi for some time, but the company now expects sales of this franchise to decline by approximately 4% to 8% each year from 2015 to 2018, primarily due to falling sales of Lantus® (insulin glargine).<sup>2</sup>

<sup>2</sup> Sanofi, Company Press Release, 29 Oct 2015.

**Table 3: Top partnering deals of 2015 by upfront consideration.**

Total Deal Value	Upfront Payment	Companies	Interest Area	Development Phase
US\$1100 M	US\$1000 M (US\$150 M cash, US\$850 M equity)	Juno Therapeutics, Celgene	T-cell therapies for cancer and autoimmune diseases with an initial focus on chimeric antigen receptor technology (CAR-T) and T-cell receptor (TCR) technologies	Various, Phase I
US\$2075 M	US\$725 M (US\$300 M cash, US\$425 M equity)	Galapagos, Gilead Sciences	JAK1-selective inhibitor filgotinib for inflammatory disease indications	Phase II
US\$2165 M	US\$640 M	Regeneron Pharmaceuticals, Sanofi	PD-1 (programmed death-1) inhibitor and other immuno-oncology antibodies	Phase I, Preclinical
US\$450 M	US\$450 M	AstraZeneca, Celgene	MEDI4736, PD-L1 (programmed death ligand-1) inhibitor programme for blood cancers	Phase III
€3900 M (US\$4259 M)	€400 M (US\$437 M)	Hanmi Pharmaceutical, Sanofi	Efpeglenatide, a long-acting glucagon-like peptide-1 receptor agonist (GLP1-RA), weekly insulin and a fixed-dosed weekly GLP-1-RA/insulin drug combination	Phase II, Phase I, Preclinical
US\$1737 M	US\$350 M	Five Prime Therapeutics, Bristol-Myers Squibb	Colony stimulating factor 1 receptor (CSF1R) antibody programme for immunology and oncology indications	Phase I
US\$1700 M	US\$300 M	Lexicon Pharmaceuticals, Sanofi	Sotagliflozin, an oral dual inhibitor of sodium-glucose cotransporters 1 and 2 (SGLT-1 and SGLT-2), for the treatment of diabetes	Phase III
US\$300 M	US\$300 M	Immunomic Therapeutics, Astellas Pharma	LAMP-vax™ products for the treatment or prevention of any and all allergic diseases in humans	Discovery
US\$1275 M	US\$250 M	Innate Pharma, AstraZeneca	IPH2201, an immune checkpoint inhibitor targeting NKG2A	Phase II
US\$250 M	US\$250 M	Merck & Co., Allergan	Small molecule oral calcitonin gene-related peptide (CGRP) receptor antagonists for the treatment and prevention of migraine	Phase II

Source: IMS PharmaDeals

Despite a slight downturn in overall partnering activity in the life sciences sector from 2014 to 2015, licensing activity for therapeutic programmes actually increased in absolute terms over this time period. Figure 8 presents an analysis of licensing activity for therapeutic programmes in 2014 and 2015 by development stage. Significantly, licensing at the discovery stage increased by more than 60% from 2014 to 2015, reflecting industry trends towards externally sourced innovation and greater efficiency in R&D, as well as a greater acceptance of scientific risk on the part of many pharmaceutical companies. Moreover, the level of licensing activity for Phase I assets increased by almost 50%, while there was a decline in the number of licensing deals for preregistration, registered/approved or launched products.

An analysis of upfront payments for licensing deals by development stage, restricted to those deals granting rights in major markets, reveals some interesting trends (Figure 9). Mean upfront payments for clinical-stage assets have increased markedly over the 2011–2015 time period. While the mean upfront payment for preclinical-stage licensing deals has increased in recent years, it has yet to return to the peak value seen in 2011, however. Of particular note is the jump in the mean upfront payment for Phase I licensing deals, which more than doubled from US\$40.15 M in 2014 to US\$83.75 M in 2015 driven by two record-breaking immuno-oncology deals. In October 2015, BMS agreed to pay Five Prime Therapeutics US\$350 M upfront to license the company’s colony stimulating factor 1 receptor (CSF1R) antibody programme (Deal no. 67223). Acknowledging its need to play catch-up in immuno-oncology, in July Sanofi licensed rights to Regeneron Pharmaceuticals’ Phase I PD-1 (programmed death-1) inhibitor SAR439684 for US\$375 M upfront as part of a broad alliance for the discovery and development of immuno-oncology antibodies (Deal no. 65799).

**Figure 8: Therapeutic licensing deals by development stage, 2014 vs. 2015.**

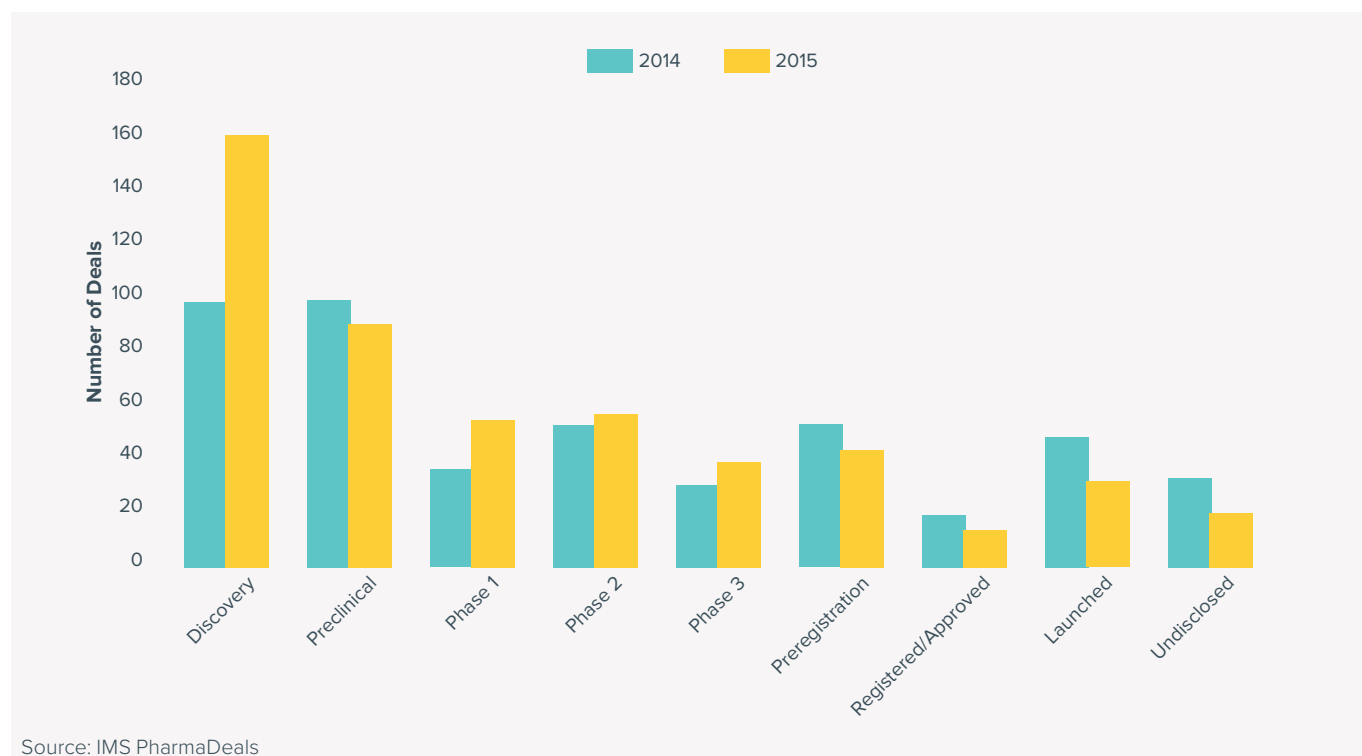
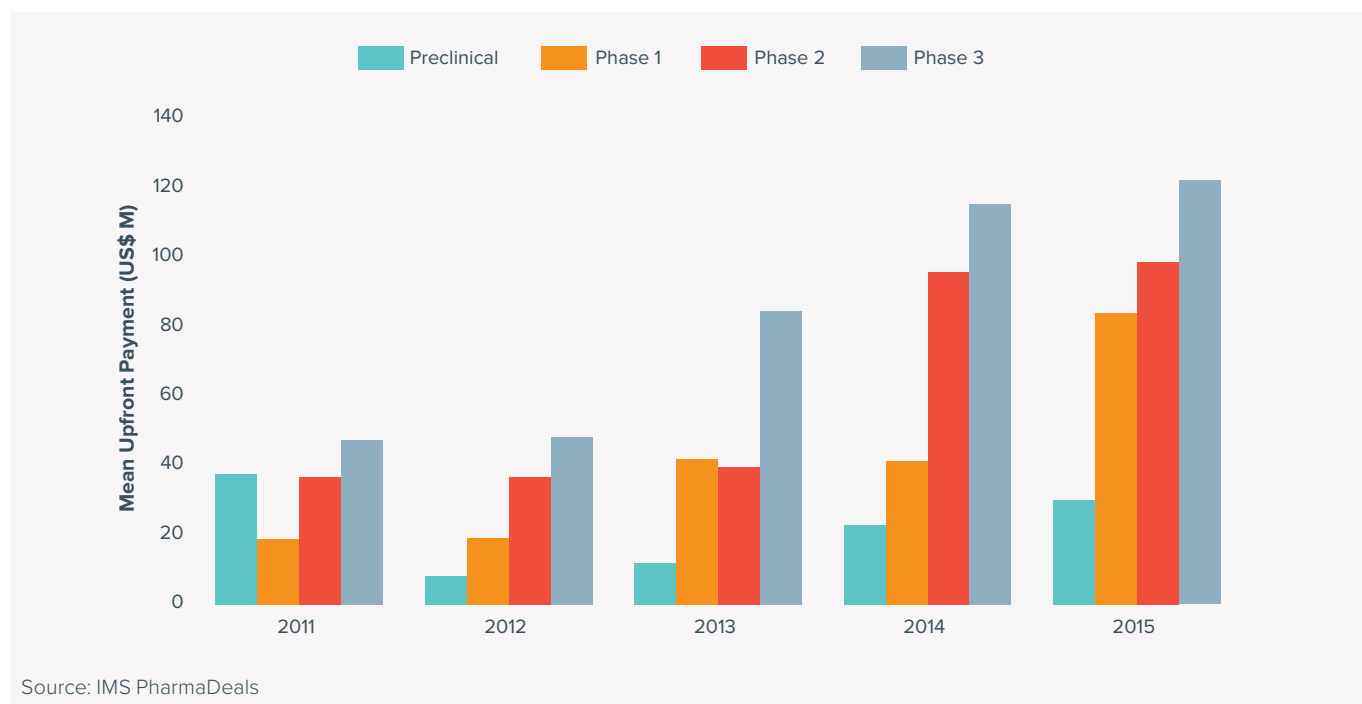


Figure 9: Mean upfront payment for licensing deals by development stage, 2011-2015.

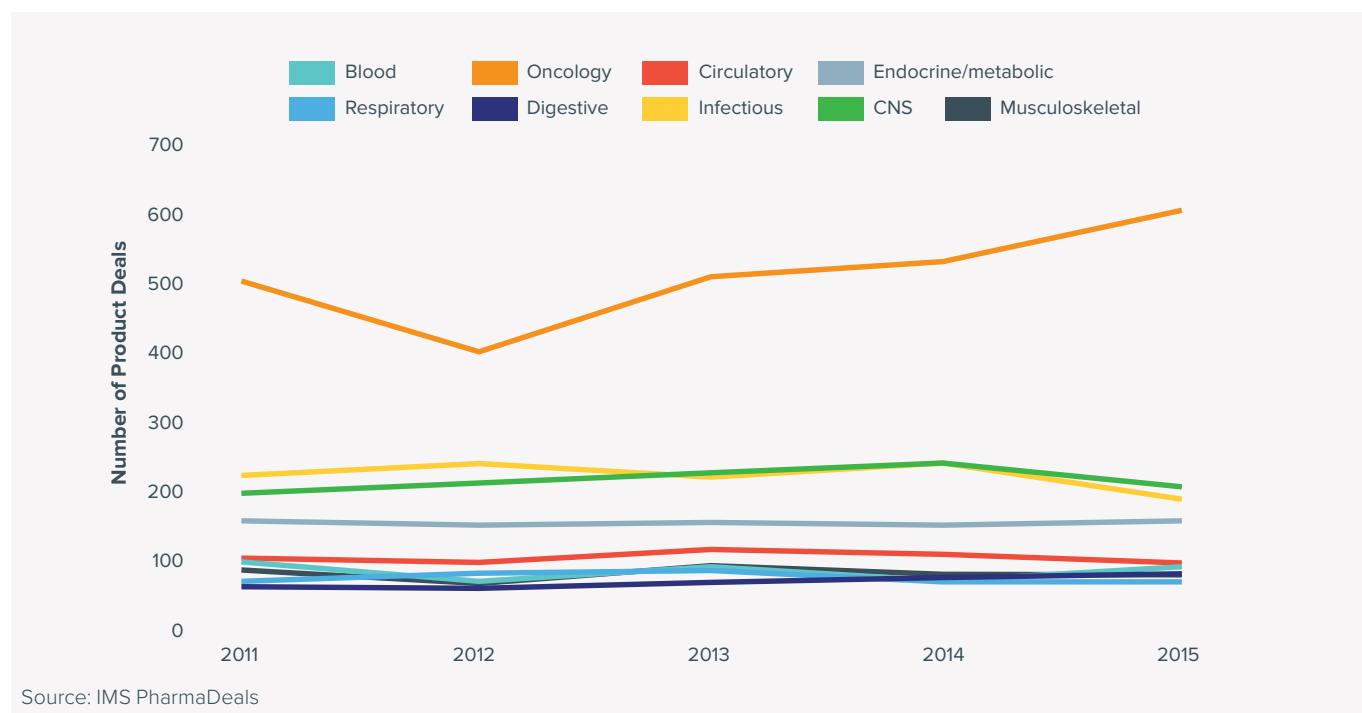


Despite 2014 seeing two Phase II licensing deals with unprecedentedly large upfront payments — Celgene paying US\$710 M upfront for Nogra Pharma’s GED-0301 (Deal no. 58425) and Pfizer paying US\$850 M upfront to co-develop and co-commercialise Merck KGaA’s MSB0010718C (avelumab) (Deal no. 62027) — the mean upfront payment for Phase II licensing deals was maintained from 2014 to 2015, with four such deals having upfront fees in excess of US\$200 M. The largest cash upfront payment for a Phase II licensing deal in 2015 was the €400 M (US\$437 M) that Sanofi agreed to pay Hanmi in order to license a portfolio of long-acting diabetes drugs, including efpeglenatide, a long-acting GLP-1 receptor agonist (GLP-1 RA) in Phase II development.

## Interest in oncology surges

As it has done ever since the IMS PharmaDeals database began in 1996, oncology represents the top therapy area for dealmaking by a considerable margin, with more than 30% of the deals signed in 2015 that were ascribed an indication involving cancer. Figure 10 presents an analysis of product deals (including product acquisitions, licensing, option to license, co-development and collaborative R&D deals) by indication area. Almost three times as many product deals in 2015 involved oncology as a therapeutic area than involved diseases of the nervous system (including mental and behavioural disorders), the second most popular therapy area for dealmaking. Infectious and parasitic diseases, endocrine, nutritional and metabolic diseases and diseases of the circulatory system comprised the third, fourth and fifth most popular therapy areas for deals signed in 2015, respectively. Despite a 4% year-on-year decline in the total number of product deals, the number of oncology product deals increased 14% from 2014 to 2015. In 2015 immuno-oncology dominated the oncology dealmaking landscape with highest level of M&A and partnering deal activity. Of the top partnering deals in oncology ranked by upfront payment, half were in the immuno-oncology space (see the Deal Trends in Immuno-Oncology 2010-2015 report published by IMS PharmaDeals for further insight and analysis).

Figure 10: Number of product deals by therapeutic area, 2011-2015.



## A revival of gene therapy

Gene therapy alliances had something of a resurgence in 2015, attracting some high profile partners and significant financials and spanning a variety of therapy areas. Somewhat impressively for a company that was founded only a year previously, in February Voyager Therapeutics partnered with Sanofi's Genzyme to advance and expand its pipeline of gene therapies for severe CNS disorders (Deal no. 63381). The collaboration combines programmes and intellectual property from both companies, with Voyager taking the lead on R&D and Genzyme, a long-time investor in the gene therapy field, having the option to license several programmes on completion of an initial proof-of concept clinical trial, with Voyager retaining US rights to certain programmes. Genzyme committed US\$100 M upfront to Voyager under the agreement, including US\$65 M in cash, a US\$30 M equity investment and additional 'in-kind contributions'.

In April, BMS established a 10-target collaboration with Dutch biotech uniQure for the development of gene therapy programmes for cardiovascular diseases, agreeing to make near-term payments of US\$100 M, including US\$50 M upfront in cash and a US\$32 M equity investment (Deal no. 64202). The deal includes uniQure's preclinical-stage gene therapy programme for congestive heart failure that is intended to restore the heart's ability to synthesise S100A1 and which the company gained with its €3 M upfront cash-and-stock acquisition of German biotech Inocard only months earlier (Deal no. 60362).

In July, Biogen and Applied Genetic Technologies (AGTC) formed a collaboration to develop gene-based therapies for multiple ophthalmic diseases, including both a clinical-stage candidate and a preclinical candidate for orphan diseases of the retina that can lead to blindness in children and adults (Deal no. 65468). Earlier in the year, Biogen formed an alliance with the San Raffaele-Telethon Institute for Gene Therapy to develop gene therapies for the treatment of both haemophilia A and B (Deal no. 63178).

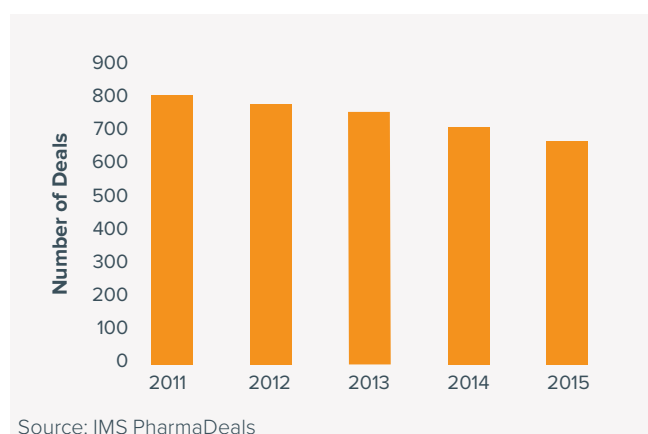


## Biological therapies drive significant collaborative R&D deal valuations

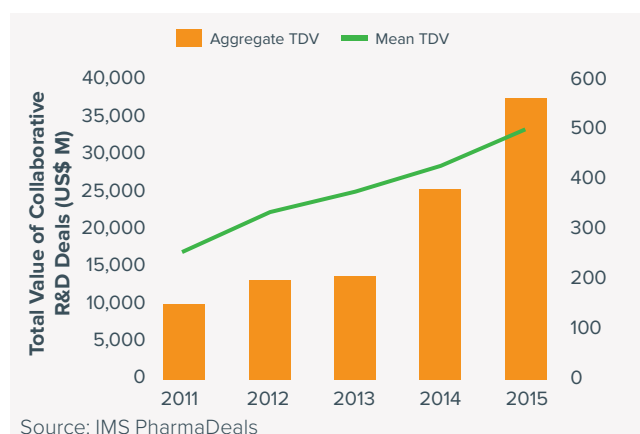
In line with the observed overall decline in dealmaking in the life sciences sector, fewer collaborative R&D deals (defined here as discovery or preclinical-stage R&D collaborations) were entered into during 2015 compared with previous years (Figure 11). Indeed, the level of collaborative R&D dealmaking, which peaked in 2011, fell by 6% from 2014 to 2015. However, the aggregate total deal value, excluding royalties, of all such deals (excluding multicomponent deals where it is not possible to split out the financial terms of the research collaboration element) has more than tripled over the past 5 years to reach an unprecedented US\$35.9 B in 2015 (Figure 12). This may reflect a number of factors, including the propensity of big pharma companies to sign broad, multitarget collaborations that have very large milestone-driven headline values that are unlikely to be realised and the desire of biotech and platform technology companies to publicise the financial terms of the deals they have been able to secure. The mean total deal value, excluding royalties, of those collaborative R&D deals with disclosed financial terms also rose in 2015 to US\$485 M, with nine deals having a headline value in excess of US\$1 B.

Although collaborative R&D deals are typically heavily back-ended in their financial structure, it is interesting to note that the observed increases in headline values for collaborative R&D deals have been accompanied by increases in the mean upfront payment for such deals. Indeed, the mean upfront payment for collaborative R&D deals rose by more than 20% from 2014 to 2015 to reach US\$36 M, in part due to three such deals having upfront payments exceeding US\$100 M (Figure 13). The largest upfront consideration was the US\$265 M that Sanofi agreed to pay Regeneron for the discovery and development component of the two companies' broad immuno-oncology alliance, which also included a licence to a Phase I PD-1 inhibitor for a separate US\$375 M upfront. Elsewhere, Celgene paid Nurix US\$150 M upfront as part of a strategic collaboration for the discovery, development and commercialisation of small molecule therapeutics that function through the ubiquitin proteasome system to modulate protein homeostasis (Deal no. 66686), while Merck Serono paid Intrexon US\$115 M as part of an alliance to develop and commercialise CAR-T cancer therapies (Deal no. 64150).

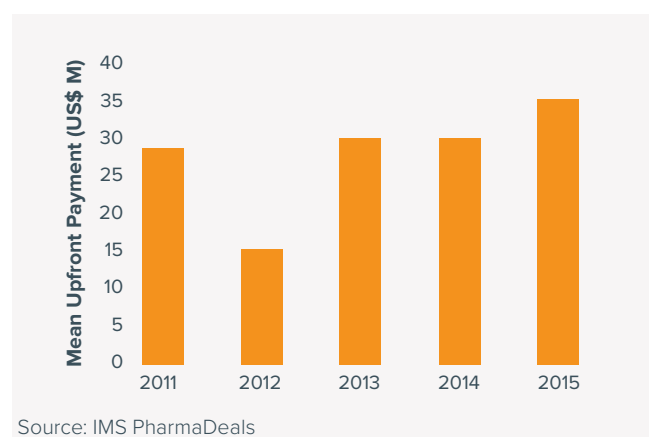
**Figure 11: Number of collaborative R&D deals, 2011-2015.**



**Figure 12: Aggregate value and mean total deal value of collaborative R&D deals, 2011-2015.**



**Figure 13: Mean upfront payment for collaborative R&D deals, 2011-2015.**



The observed upward shift in upfront payments for R&D collaborations likely reflects fierce competition for attractive early-stage assets and discovery platforms amongst pharmaceutical companies keen to secure the long-term growth prospects of key franchises.

Table 4 presents the top 10 collaborative R&D deals of 2015 as ranked by total potential deal value. It is interesting to note that the majority of the deals on the list relate to biological therapies, with appearances by gene therapies, cell therapies, RNA-based therapeutics and bispecific antibodies.

**Table 4: Top therapeutic collaborative R&D deals of 2015 by total deal value.**

Total Deal Value	Upfront Payment	Companies	Interest Area
US\$4090 M	US\$65 M	Ionis Pharmaceuticals, AstraZeneca	Antisense therapies for treating cardiovascular and metabolic diseases, and renal diseases
US\$2304 M	US\$50 M	uniQure, Bristol-Myers Squibb	Gene therapies for cardiovascular diseases
US\$1923 M	Undisclosed	Heptares, Pfizer	Potential new medicines directed at up to 10 G protein-coupled receptor (GPCR) targets across multiple therapeutic areas
US\$1745 M	US\$45 M	Xencor, Amgen	Bispecific antibody therapeutics in the areas of cancer immunotherapy and inflammation
US\$1560 M	US\$60 M (including near-term milestone payments)	BioNTech, Sanofi	Up to five cancer immunotherapies, each consisting of a mixture of synthetic mRNAs
US\$1193 M	US\$23 M	Halozyme Therapeutics, AbbVie	Products combining AbbVie compounds with Halozyme's ENHANZE™ platform
US\$1110 M	US\$60 M	Kite Pharma, Amgen	Next-generation of chimeric antigen receptor (CAR) T-cell immunotherapies
US\$941 M	US\$115 M	Intrexon, Merck Serono	CAR-T cancer therapies
US\$835 M	US\$35 M	Ionis Pharmaceuticals, Janssen Biotech	Antisense drugs to treat autoimmune disorders of the gastrointestinal tract
US\$825 M	US\$25 M	Halozyme Therapeutics, Eli Lilly	Products combining Lilly compounds with Halozyme's ENHANZE™ platform

Source: IMS PharmaDeals

Ionis Pharmaceuticals' deal with AstraZeneca to discover and develop antisense therapies for treating cardiovascular/metabolic diseases and renal diseases heads the list (Deal no. 65851). As part of the agreement, Ionis (which until earlier in 2015 was known as Isis Pharmaceuticals) granted long-standing partner AstraZeneca an exclusive licence to a preclinical programme and the option to license a drug for each target advanced under this research collaboration. Earlier in the year and in a further validation of its RNA-targeted technology platform, Ionis partnered with J&J's Janssen Biotech to discover and develop antisense drugs that can be locally administered, including via oral delivery, for the treatment of autoimmune disorders of the gastrointestinal tract (Deal no. 62791). The deal provides Janssen with the option to license a drug from each of the three programmes once a development candidate has been identified. Ionis is thus far the only company to have successfully advanced antisense therapeutics to market, most recently Kynamro® (mipomersen), which was developed in collaboration with Sanofi's Genzyme and which was approved by the FDA in January 2013 for the treatment of patients with homozygous familial hypercholesterolaemia (Deal no. 29357).

Halozyme Therapeutics appears on the list twice, thanks to its deals with AbbVie (Deal no. 64976) and Eli Lilly (Deal no. 68641) to develop and commercialise products combining compounds from each company with Halozyme's ENHANZE™ platform. The ENHANZE platform is based on a recombinant human hyaluronidase enzyme (rHuPH20) that temporarily degrades hyaluronan to aid in the dispersion and absorption of other injected therapeutic drugs. Halozyme already has a sizeable roster of big pharma partners, including Pfizer (Deal no. 50167), Roche (Deal no. 33875), Baxalta (Deal no. 28269) and Janssen (Deal no. 62522).

## Orphan drugs remain sought after

2015 saw more orphan drug approvals in the US than any other year on record; 21 of the 45 drugs approved by the FDA's Center for Drug Evaluation and Research in 2015 were approved to treat rare diseases affecting 200,000 or fewer Americans. Unsurprisingly, a number of pharmaceutical and biotech companies sought out new opportunities in the rare disease field in 2015 via acquisitions or alliances. As was also the case in 2014, Shire was a serial acquirer, obtaining orphan drug assets with its purchases of NPS Pharmaceuticals (Deal no. 62980), Meritage Pharma (Deal no. 63604) and Dyax. In August and in a move aimed at bolstering its burgeoning fibrotic disease pipeline, BMS obtained the exclusive right to acquire privately held Promedior and its Phase II asset PRM-151, a recombinant form of human pentraxin-2 protein (rhPTX-2) that has been granted Orphan Drug Designation in the US and Europe for the treatment of idiopathic pulmonary fibrosis and myelofibrosis (Deal no. 66346). Total payments to Promedior under the agreement could reach US\$1.25 B, including US\$150 M upfront in cash. Earlier in the year, BMS also forged academic research collaborations in the fibrosis field with the California Institute for Biomedical Research (Deal no. 62776) and the Medical University of South Carolina (Deal no. 65543).

## Outlook for 2016

2015 saw the return of the mega-merger and the first quarter of 2016 has already seen some significant M&A activity led by Shire's US\$32 B acquisition of Baxalta, which will create the world's largest rare disease company by sales (Deal no. 68973). Speculation remains that the M&A wave will slow down, however, amid a climate of financial uncertainty, a weakening dollar and declining share prices. Nevertheless, companies such as Gilead and J&J are sitting on sizeable cash piles and the expectation remains that such companies will sign some significant deals in 2016, be they acquisitions or alliances. Pharmaceutical companies will continue to look to biotechs and academia for new sources of innovation, thus driving robust early-stage dealmaking. The high level of deal activity in the highly competitive immuno-oncology field is expected to continue in 2016 and beyond, with more M&A deals expected as the field evolves.

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