IMS PharmaDeals: Review of 2016

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Market turbulence and political uncertainty drive dealmaking slowdown

Deal activity in the life sciences sector slowed in 2016 amid a climate of political and economic uncertainty. Indeed, for many of the metrics analysed in this review, deal activity in 2016 failed to live up to 2015, with deal volumes and mean total potential deal values falling for both M&A deals and licensing agreements. That is not to say that 2016 was a particularly bad year for dealmaking, however, as it surpassed 2012, 2013 and 2014 on a number of measures. Nevertheless, despite healthy balance sheets, many companies were wary of big-ticket M&A owing to concerns of overinflated valuations and uncertainty surrounding the future policies of the new political administration in the US.

The venture capital market remained accessible to early-stage biotechs, although IPO market conditions were poor for many companies. The pursuit of growth continued to be a key influencer of deal activity and companies were once again willing to pay sizeable premiums to acquire key commercial and late-stage assets. For the fourth year running, AstraZeneca was the most prolific dealmaker, albeit only by a small margin ahead of Johnson & Johnson, helped by an extensive roster of externalisation deals. In terms of deal spend, Shire was the top ranked company in 2016 thanks to its US$32 B takeover of Baxalta. Oncology remained the leading therapeutic area for partnering deals and the immuno-oncology field in particular saw significant investment in R&D alliances.

Appetite for M&A diminishes

The decline in deal activity in the life sciences sector that has been observed in recent years continued in 2016. A review of the IMS PharmaDeals database of publicly disclosed deal activity reveals that the number of agreements signed, excluding standalone research grants, decreased by approximately 14% from 2015 to 2016 (Figure 1). Indeed, after peaking in 2013, deal activity is now at its lowest level for 5 years. There are likely a number of factors contributing to this decline, perhaps most significantly a turbulent political and economic climate. Figure 2 shows that dealmaking slowed as the US presidential election date approached due to uncertainty of the result and following Hilary Clinton's election campaign rhetoric against high drug prices, which had a pronounced negative impact on biopharma valuations. Indeed, the Nasdaq Biotechnology Index ended the year 19.1% down on where it started in January 2016 and has fallen roughly 30% from its peak in July 2015. While market conditions were poor for companies seeking an IPO in 2016, with many biotech companies that gained a listing subsequently trading below their offer price, the venture capital market for early-stage companies remained robust. VCs invested more than US$5.4 B in biotech through Q3 2016,[1] less however than the equivalent period in 2015, a record year for biotech venture financing. What is more, well-funded biotech companies that raised significant capital in 2015 were able to be more discerning in the deals that they chose to pursue. In recent years, large pharmaceutical and biotech companies have accumulated sizeable portfolios of deals and alliances, and while the need for new near-term and long-term revenue generators persists, such companies are very selective in the types of assets they wish to pursue. Indeed, many such companies are newly streamlined after having undertaken significant restructuring in recent years – swapping, divesting and acquiring assets – and are now focused on integrating these, leaving less resource for new deals.

-14%

The number of agreements signed, excluding standalone research grants, decreased by approx. 14% from 2015 to 2016

Figure 1: Number of deals (excluding funding awards), 2012-2016

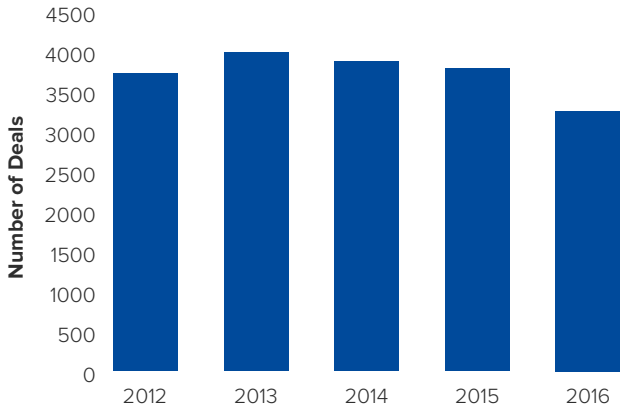
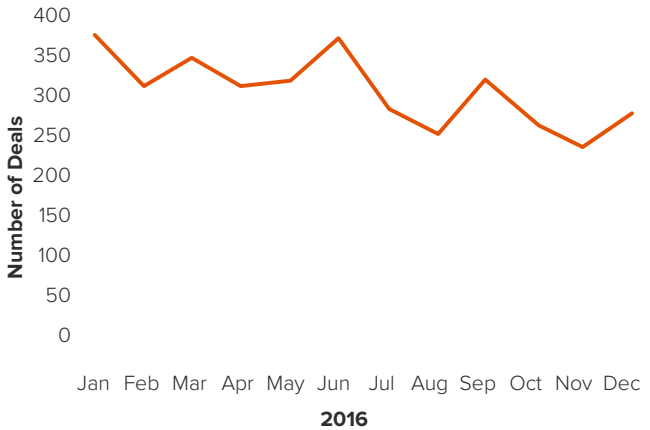


Figure 2: Deals signed in 2016 by month



Source: IMS PharmaDeals

[1] PricewaterhouseCoopers, National Venture Capital Association MoneyTree™ Report

At the beginning of 2016, we speculated that the M&A wave that peaked in 2014 – an unprecedented year for industry consolidation in terms of deal valuations – would slow down, amid a climate of financial uncertainty, a weakening dollar and declining share prices. This view was supported by the subsequent collapse of Pfizer's US$160 B mega-merger with Allergan following the hasty implementation of new tax legislation by the US government aimed at thwarting so-called tax inversions (Deal no. 68062). However, despite the continuing downturn in overall deal activity in the life sciences sector, the volume of M&A deals announced in 2016 (defined here as Mergers, Business Acquisitions and Divestments, signed but not necessarily completed) was broadly on a par with the equivalent figure in 2015, down only 3% (Figure 3). At US$216.1 B, the aggregate total value of all M&A deals signed in 2016 was 11% lower than the corresponding figure for 2015 (which no longer includes the US$160 B Pfizer/Allergan merger) and 38% less than the high of US$349.7 B achieved in 2014. It must be noted that this analysis uses potential total deal value figures and includes contingent consideration that might not be paid. Interestingly, the mean total deal value for M&A deals decreased only 0.1% from US$1025 M in 2015 to US$1024 M in 2016 (Figure 4), although the median total deal value actually fell 15% to US$105 M in 2016 (Table 1). Pharmaceutical and biotech valuations fell in 2016 under a drug pricing cloud fuelled by fears of future reforms in the US by the new political administration. To some extent, this was a correction of the overinflated valuations that had accompanied the availability of cheap debt finance. One possible explanation for the M&A slowdown is that the biggest companies are waiting for valuations to become more realistic before they commit to deals. Moreover, companies regarded as attractive takeover targets are seemingly few and far between and those that fall in the industry's sweet spot – companies with marketed and high potential late-stage assets – attract considerable interest, thus driving up premiums. Pfizer's acquisition of the highly prized Medivation (Deal no. 72980), following a hostile approach by Sanofi and reported interest from many of its peers, is a case in point. At US$81.50 per share, Pfizer paid a premium of 118%, one of the highest in 2016, to get its hands on Medivation.

-11%

The aggregate total value of all M&A deals signed in 2016 was 11% lower than the equivalent figure for 2015

Table 1: Aggregate, mean and median values of M&A deals, 2015 vs. 2016

	2015	2016	Change
Aggregate value of all M&A deals	US$241,943 M	US$216,135 M	-11%
Mean deal value	US$1025 M	US$1024 M	-0.1%
Median deal value	US$123.3 M	US$105 M	-15%

Source: IMS PharmaDeals

Figure 3: Number and aggregate total value of M&A deals, 2012-2016

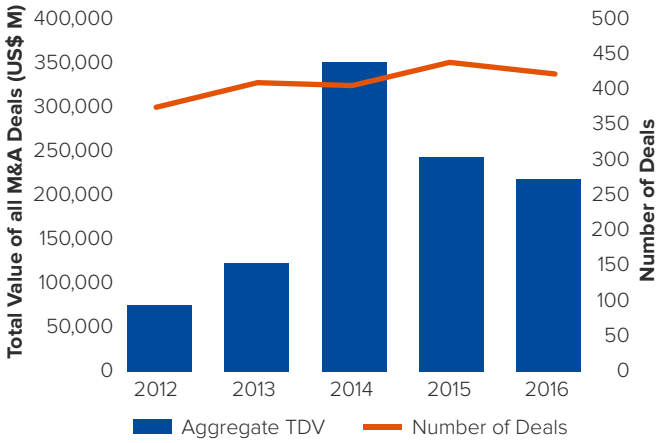
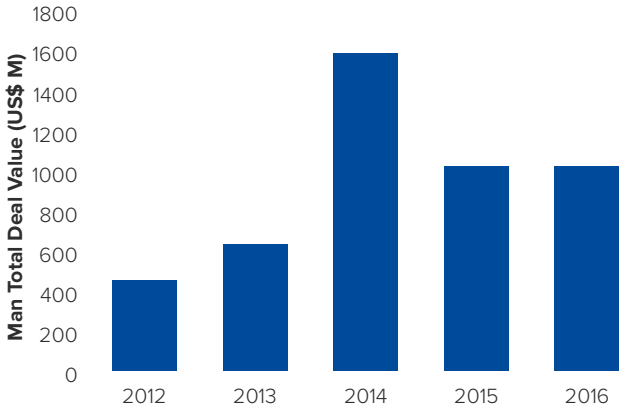


Figure 4: Mean total deal value of M&A deals, 2012-2016



Source: IMS PharmaDeals

The largest M&A deal of 2016 was Shire's US$32 B cash and stock purchase of Baxalta, which put an end to a 6-month pursuit (Deal no. 68973). The merger created the largest rare disease company by sales, doubling the size of Shire's existing business in this area and giving the company a dominant position in the haemophilia treatment market, as well as a nascent oncology franchise. The deal also gave Shire access to new markets owing to Baxalta's wider geographic reach as well as tax benefits arising from moving Baxalta's business into its lower tax Irish domicile. There are risks associated with the takeover, however, given the competitive threat faced by Baxalta's haemophilia franchise, which had been estimated to generate approximately 70% of the company's operating profit. Sales of Baxalta's haematology products fell 6% to US$884 M in the first full quarter following the close of the deal.

US$32B

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Big pharma appetite for M&A was muted in 2016, with only Pfizer, Sanofi and Johnson & Johnson (J&J) signing multibillion dollar deals and only Pfizer doing so in order to gain innovative pharmaceutical assets. After the collapse of its merger with Allergan in April 2016, Pfizer rallied by signing high-premium deals to acquire Anacor Pharmaceuticals for US$5.2 B (Deal no. 71316) and Medivation for US$14 B. The Anacor purchase, for a 55% premium, was aimed at boosting the prospects of the company's immunology and inflammation portfolio and subsequently did just that when Anacor's flagship asset crisaborole, a topical phosphodiesterase-4 (PDE4) inhibitor, was approved by the US FDA in December 2016 for the treatment of mild-to-moderate atopic dermatitis. Pfizer believes that the drug could reach or exceed peak year sales of US$2 B. The key driver of the Medivation acquisition, the largest deal to be announced in H2 2016, was the company's marketed prostate cancer therapy Xtandi® (enzalutamide), which is co-promoted with Astellas Pharma in the US and marketed solely by Astellas in other markets (Deal no. 34025). Pfizer also gained two late-stage targeted cancer therapies: talazoparib and pidilizumab. The high price, equating to approximately 18 times current revenue, reflected the fact that Medivation was in a very strong negotiating position.

Allergan was itself a serial acquirer in 2016, agreeing to acquire nine companies over the course of the year and four in September alone. At the beginning of the month, the company acquired RetroSense Therapeutics and thereby gained global rights to RST-001, a gene therapy in Phase I/II development for retinitis pigmentosa (Deal no. 73293). The following week, it agreed to acquire Vitae Pharmaceuticals for approximately US$639 M in order to access Phase II drug candidates for dermatology indications (Deal no. 73509). It subsequently made a bold entry into the non-alcoholic steatohepatitis (NASH) market with the complementary acquisitions of US-based Tobira Therapeutics (Deal no. 73620) and UK-based Akarna Therapeutics (Deal no. 73633). The key driver of the Tobira deal, which is potentially worth up to US$1.7 B was the Phase III-ready asset cenicriviroc, an immunomodulator and dual inhibitor of the CCR2 and CCR5 chemokine receptors. The takeover of Akarna gave Allergan access to AKN-083, a farnesoid X receptor (FXR) agonist for which an IND was planned in early 2017, for a comparatively small upfront fee of US$50 M (subject to certain adjustments) plus undisclosed clinical, regulatory and commercial milestone payments. Allergan also acquired medical dermatology and aesthetic medicine company Anterios in a potential US$477.5 M deal (Deal no. 68891), topical dermatology company Topokine Therapeutics for US$85 M upfront (Deal no. 70912), eye care biotech ForSight VISION5 for US$95 M upfront (Deal no. 72837), neurodegenerative disorder specialist Chase Pharmaceuticals for up to US$1000 M (Deal no. 75048) and regenerative medicine company LifeCell for US$2.9 B (Deal no. 75655).

Combined, the top 10 business acquisitions of 2016, as ranked by total potential deal value and recorded in the IMS PharmaDeals database, had an aggregate value of US$120.5 B, a figure 16% lower than the combined value of the top 10 M&A deals of 2015 and equivalent to 56% of the aggregate value of all M&A deals signed during 2016 (Table 2). Interestingly, only three of the top 10 acquisitions of 2016 had a deal value in excess of US$10 B, while there were five US$10 B-plus deals signed in 2015. Moreover, 32 M&A deals in 2015 had a value of between US$1 B and US$10 B, compared to 38 in 2016. The top 10 deals list spans a variety of industry sectors, including medical devices, diagnostics and generic, OTC and prescription pharmaceuticals. Abbott features twice in the top 10 M&A deals list, thanks to its US$25 B acquisition of St. Jude Medical (Deal no. 71083), aimed at bulking up the company's medical device business to enable it to better compete with the likes of Medtronic and Boston Scientific, and its US$5.8 B agreement to buy point-of-care diagnostics developer Alere (Deal no. 69338), which is far from certain to complete. In April 2016, Abbott tried to terminate the takeover citing concerns relating to the delay in Alere filing its 2015 annual report as well as government investigations into the company. This request was rejected by Alere, however. In December, Abbott filed a complaint in the Delaware Court of Chancery seeking to terminate the deal and alleging that Alere has lost significant value due to 'numerous damaging business developments that occurred following the merger agreement'. Some analysts believe this could be a tactic for Abbott to negotiate a reduction in the purchase price.

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Table 2: Top acquisitions of 2016 ranked by total deal value

Total Deal Value	Companies	Deal Driver
US$32 B	Shire, Baxalta	Market leadership in rare diseases
US$25 B	Abbott, St. Jude Medical	Portfolio of cardiovascular medical devices
US$14 B	Pfizer, Medivation	Xtandi® (enzalutamide), an anti-androgen for metastatic castration-resistant prostate cancer
US$9.9 B	Mylan, Meda	Speciality generic and OTC pharmaceuticals, European operations
US$9.8 B	AbbVie, Stemcentrx	Rovalpituzumab tesirine (Rova-T) for relapsed small-cell lung cancer
US$7.4 B	Sanofi, Boehringer Ingelheim	Consumer healthcare business
US$5.9 B	Toshiba, Canon Medical Systems	Medical equipment
US$5.8 B	Abbott, Alere	Market leadership in point-of-care diagnostics
US$5.5 B	Lonza Group, Capsugel	Expand reach of contract development and manufacturing organisation and products businesses
US$5.2 B	Pfizer, Anacor Pharmaceuticals	Crisaborole, a nonsteroidal topical phosphodiesterase-4 (PDE4) inhibitor under US regulatory review for atopic dermatitis

Source: IMS PharmaDeals

AbbVie's takeover of privately held Stemcentrx is the only M&A deal of the top 10 to involve significant contingent consideration (Deal no. 71057). The company paid US$2 B in cash and US$3.8 B in stock for Stemcentrx's late-stage antibody-drug conjugate (ADC) rovalpituzumab tesirine (Rova-T) plus four additional molecules being developed for solid tumours. Former Stemcentrx shareholders also stand to receive up to US$4 B if certain development and regulatory milestones are achieved. Rova-T is a biomarker-specific therapy that is derived from cancer stem cells and is targeted to delta-like protein 3 (DLL3), which is expressed in more than 80% of small-cell lung cancer (SCLC) tumours but which is not present in healthy tissue. AbbVie saw its share price dip in June 2016, however, after underwhelming Phase I clinical data for Rova-T were presented at the American Society of Clinical Oncology annual meeting, leading analysts to question the high deal valuation.

Consolidation in the speciality pharma sector was a key M&A trend in 2014 and 2015 but slowed in 2016 as the deficiencies in Valeant Pharmaceuticals' aggressive growth by acquisition strategy became all too apparent. One notable exception was Mylan's SEK83.6 B (US$9.9 B, inclusive of debt) purchase of Meda, a deal that came at the third attempt and which added the Swedish company's European operations to Mylan's existing business (Deal no. 69514). Prior to the acquisition, Meda had been responsible for European sales of Mylan's biggest-selling product EpiPen® (epinephrine) (Deal no. 38640). The takeover was not very well received, with shares of Mylan closing down 18% on news of the cash-and-stock deal and analysts questioning the 92% premium. The deal came 3 months after Mylan failed in its US$26 B hostile bid for smaller rival Perrigo and was followed by the US$1 B purchase of the topicals-focused speciality and generics business of Renaissance Acquisition Holdings (Deal no. 71292).

Externalisation helps AstraZeneca retain its dealmaking lead

For the fourth year running, AstraZeneca has retained its title as the most prolific pharmaceutical dealmaker with 54 publicly disclosed deals, down 31% from the 78 deals announced the previous year (Figure 5). J&J takes second place in the deal activity rankings with 52 deals, closely followed by Roche and Pfizer with 49 and 48 deals, respectively. While Roche essentially maintained its level of deal activity from 2015 to 2016, Pfizer signed 45% more deals in 2016 than in 2015, no doubt a consequence of the failure of its mega-merger with Allergan in April 2016.

More than 30% of AstraZeneca's deals in 2016 involved the externalisation of legacy or non-core assets as part of the company's strategy to address the revenue gap left by key patent expiries and prioritise resources on key growth areas. The largest of these was the divestment of its late-stage small molecule anti-infectives business, primarily outside the US, to Pfizer for up to US$1575 M, including US$550 M upfront (Deal no. 73208). The deal included development and commercialisation rights to Zavicefta™ (ceftazidime-avibactam), which was approved in the EU in June 2016 for the treatment of multidrug-resistant Gram-negative infections, the marketed drugs Merrem™/Meronem™ (meropenem) and Zinforo™ (ceftaroline fosamil), and the clinical-stage assets aztreonam-avibactam (ATM-AVI) and CXL. Other notable externalisation deals in 2016 include a US$115 M upfront licensing agreement with Leo Pharma for global rights to the anti-IL-13 (anti-interleukin-13) monoclonal antibody tralokinumab in skin diseases (Deal no. 72266), a US$100 M upfront licensing agreement with Ironwood Pharmaceuticals for the US rights to Zurampic® (lesinurad) (Deal no. 70976), the sale of ex-US rights to its anaesthetics portfolio to South Africa-based Aspen for an upfront consideration of US$520 M (Deal no. 71789), a US$250 M upfront out-licensing deal with Allergan for global rights to MEDI2070, an anti-IL-23 monoclonal antibody in Phase IIb development for moderate-to-severe Crohn's disease (Deal no. 73914), and the divestment of ex-US rights to Rhinocort Aqua® (budesonide), a nasal spray approved for allergic and non-allergic rhinitis, to J&J's Cilag for US$330 M (Deal no. 74044). In total, AstraZeneca raised US$2.7 B in upfront cash from its divestment and out-licensing deals in 2016.

AstraZeneca's other deals were predominantly early-stage R&D alliances in its core therapeutic areas, with the most notable being a collaboration with Bicycle Therapeutics for the identification and development of bicyclic peptides for the treatment of respiratory, cardiovascular and metabolic diseases that could be worth more than US$1 B in payments if all planned programmes reach the market (Deal no. 75228). Unlike in 2015, the company failed to conclude any high-profile in-licensing deals in 2016.

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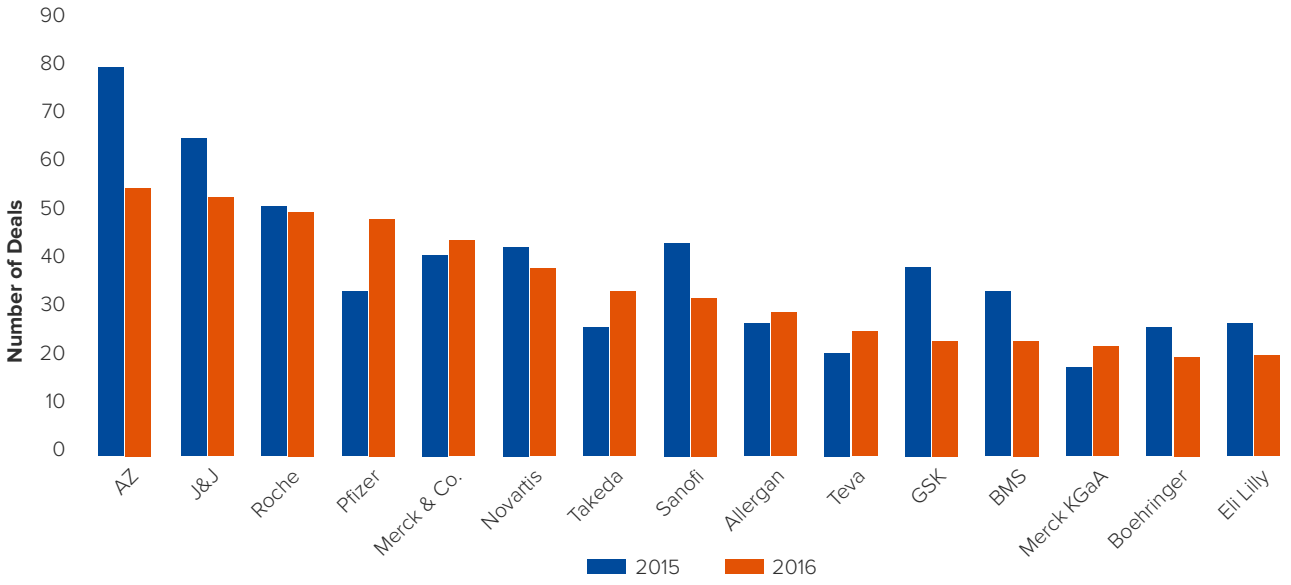
Figure 5: Most prolific dealmakers, 2015 vs. 2016



Source: IMS PharmaDeals

In the midst of a significant overhaul of its R&D operations, Takeda Pharmaceutical stepped up its dealmaking activity in 2016, in an attempt to offset declining sales in oncology with the impending arrival of generic competition on Velcade® (bortezomib), which is expected from 2017 after a US court ruled that a formulation patent on the drug expiring in 2022 was invalid. As a result, sales of the drug are expected to decline at a CAGR of -17% over 2016-2020, according to an analyst consensus forecast (IMS Health Analytics Link). The company has reportedly set aside US$15 B to spend on deals in its core areas of oncology, gastrointestinal disorders and neurological diseases. In February, Takeda expanded its relationship with Mersana Therapeutics by licensing rights to the company's lead preclinical ADC, XMT-1522, outside the US and Canada in a deal potentially worth up to US$830 M (Deal no. 69361). The Japanese company also has an option-based research collaboration with EnGeneIC to develop EDV™-based immunomodulatory therapies for oncology (Deal no. 74052), obtained ex-US commercialisation rights to Cx601, an injectable allogeneic mesenchymal stem cell-based therapy under regulatory review in the EU for complex perianal fistulas in patients with Crohn's disease, from TiGenix (Deal no. 72134), and partnered with UK-based Crescendo Biologics for the discovery, development and commercialisation of Humabody®-based therapeutics for undisclosed cancer indications in a deal potentially worth up to US$790 M (Deal no. 74122). Humabodies are based on VH domain antibody fragments and have certain advantages over IgG-based therapeutics, including improved therapeutic index.

In the midst of a significant overhaul of its R&D operations, Takeda stepped up its dealmaking activity in 2016, in an attempt to offset declining sales in oncology

J&J's largest deal by some margin was its US$4325 M cash acquisition of Abbott Medical Optics (Deal no. 73659). The company began the year by announcing 22 collaborations across its consumer, medical devices and pharmaceutical divisions, including an exclusive licence agreement with Chia Tai Tianqing Pharmaceutical to develop, manufacture and commercialise, outside of China, undisclosed immune-modulating agents to treat chronic hepatitis B virus (HBV) infection (Deal no. 68930), a collaboration with Enterome for the discovery of novel targets and bioactive molecules from the gut microbiome for the potential development of therapeutic solutions to Crohn's disease (Deal no. 68859) and

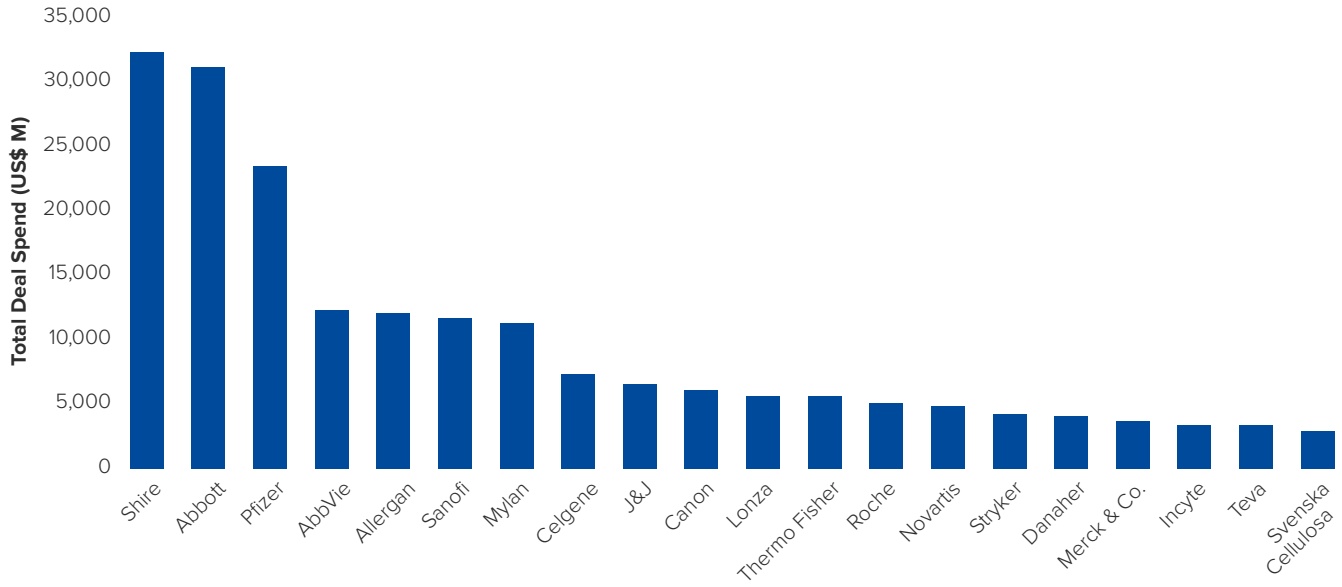
a collaboration with Eureka Therapeutics to develop a T-cell engaging antibody therapy targeting intracellular oncogenes for the potential treatment of lung cancer (Deal no. 69021). Arguably J&J's most significant pharmaceutical deal was the licensing agreement between its Janssen Biotech division and existing partner MacroGenics for global rights to MGD015, a preclinical DART® (dual-affinity re-targeting) molecule for the potential treatment of various haematological malignancies and solid tumours (Deal no. 71337). The deal came less than 18 months after the two companies partnered for the development of MGD011 for multiple B-cell malignancies (Deal no. 62657) and was in part driven by the potential synergy that exists between MGD011 and MGD015 in tumour types expressing both of the antigens targeted by these drug candidates. For J&J, the deal continued the company's pipeline expansion efforts in oncology. In April 2016 and in a deal worth up to US$500 M, Janssen licensed ex-Japan rights to the poly(ADP ribose) polymerase (PARP) inhibitor niraparib in prostate cancer from Tesaro (Deal no. 70651). Otherwise, J&J's deals were very much biased towards the early stages of development.

Merck & Co. completed a number of small bolt-on acquisitions in 2016 aimed at bolstering the company's development pipeline. In January 2016, it acquired UK-based IOmet Pharma and its preclinical pipeline of IDO (indoleamine-2,3-dioxygenase 1), TDO (tryptophan-2,3-dioxygenase) and dual-acting IDO/TDO inhibitors for US$150 M upfront in order to expand its immuno-oncology R&D endeavours (Deal no. 68963). The deal also includes additional milestone payments of up to US$250 M if certain clinical and regulatory milestones are achieved. In the same month, Merck entered into a strategic agreement with Quartet Medicine for the development of Quartet's pipeline of novel small molecule drugs modulating the tetrahydrobiopterin (BH4) pathway (Deal no. 68863). As part of this deal, Merck obtained an exclusive option to purchase Quartet for up to US$575 M. Moreover, in order to expand its pipeline of drug candidates for neurogenic conditions, in June Merck agreed to acquire privately held Afferent Pharmaceuticals for an upfront payment of US$500 M plus up to an additional US$750 M associated with the attainment of certain clinical development and commercial milestones for multiple indications and candidates (Deal no. 71755). Afferent's lead asset, AF-219, is a selective small molecule P2X3 antagonist in Phase IIb development for refractory chronic cough. Merck's high level of dealmaking in 2016 is in part a consequence of it signing a number of clinical trial agreements to investigate Keytruda® (pembrolizumab) in combination with other external oncology assets.

With 12 deals, Celgene fails to make the top dealmakers list. However, the company is reaping the rewards of its previous partnering, having exercised several options in 2016 that it had been granted under earlier deals. In doing so, Celgene has added commercial rights outside North America and China to Juno Therapeutics' CD19-directed product candidates (Deal no. 65423), ex-US rights to Abide Therapeutics' endocannabinoid system modulator ABX-1431 (Deal no. 57336), certain rights to Northern Biologics' MSC-1, a first-in-class antibody that targets leukaemia inhibitory factor (LIF) (Deal no. 64496), and Triphase Accelerator's marizomib, which is in clinical development for glioblastoma and relapsed and/or refractory multiple myeloma (Deal no. 56308), to its development pipeline. Celgene also exercised a buyout option it obtained in 2013 to acquire Acetylon Pharmaceuticals and with it worldwide rights to Acetylon's selective HDAC6 (histone deacetylase 6) inhibitor programmes and IP in oncology, neurodegeneration, and autoimmune disease, including its drug candidates citarinostat (ACY-241) and ricolinostat (ACY-1215) (Deal no. 53842).

Figure 6 presents an analysis of the leading companies as ranked by the aggregate total deal value of each company's deals in 2016, excluding those deals where the company is itself receiving payment e.g. out-licensing agreements or divestments. Financials associated with the exercise of options granted in earlier years are not included in the analysis. As licensing and collaborative deals are included in the analysis, the total deal spend is unlikely to be wholly realised in some cases. Nineteen of the 20 companies pledged to spend more than US$3 B on deals in 2016. Shire tops the rankings thanks to its takeover of Baxalta. The company also signed a US$90 M upfront in-licensing deal with Pfizer for PF-00547659, a fully human monoclonal antibody in Phase II development for moderate-to-severe inflammatory bowel disease (Deal no. 71802). The other top positions are occupied by companies that are also to be found in the top M&A deals list.

Figure 6: Top 20 companies ranked by aggregate total value of all disclosed deals in 2016 (excluding out-licensing deals and divestments by such companies)



Source: IMS PharmaDeals

Decline in licensing activity continues

Licensing activity in the life sciences sector has fluctuated in recent years, peaking in 2013 and falling 6% from 2015 to 2016 to reach its lowest level for 5 years (Figure 7). The mean total deal value, excluding royalties, for licensing deals with disclosed financial information, which peaked at US$348 M in 2014, also fell by 8% from 2015 to 2016 to reach US$295 M. The median total deal value of all licensing deals, however, actually increased by 1% from 2015 to 2016 to reach US$101 M. While licensing deal values are typically inflated by 'biodollars' that are unlikely to be paid, cash upfront payments offer a much better barometer of trends in licensing deal terms. The mean cash upfront payment for licensing deals signed in 2016 was US$37.3 M, a drop of 8% on the figure achieved in 2015 and down 26% on the high of US$50.3 M reached in 2014 (Figure 8). Interestingly, however, the median cash upfront payment for licensing deals recorded in the IMS PharmaDeals database, which was US$10 M in both 2014 and 2015, actually rose to US$12 M in 2016.

2016 saw only six licensing deals with upfront payments greater than or equal to US$200 M, while there were ten such deals in 2015. The 2014 values are also unduly influenced by licensing deal terms of unprecedented magnitude, such as the US$1000 M upfront that Merck 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, our analysis of licensing deals in the life sciences sector demonstrates that mean upfront payments have doubled over the 5-year period from 2012 to 2016.

The highest upfront payments in 2016 were reserved for late clinical-stage or on-market assets across a variety of therapy areas. Surprisingly, oncology does not feature at the top of the list, perhaps due to a dearth of late-stage available assets in this therapy area, driving M&A over licensing

Figure 7: Number of licensing deals, 2012-2016

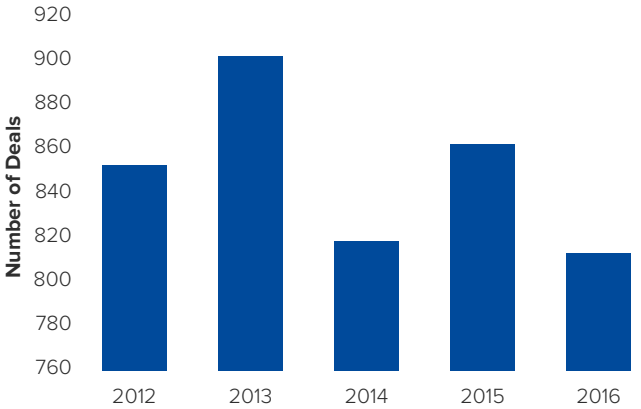
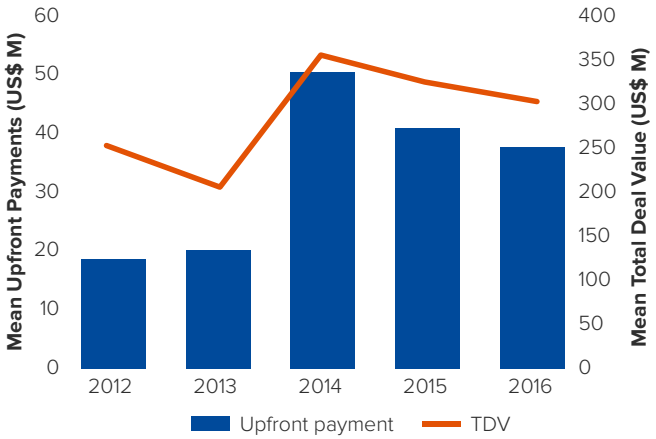


Figure 8: Mean total deal value and mean upfront payment for licensing deals, 2012-2016



Source: IMS PharmaDeals

The highest upfront payments in 2016 were reserved for late clinical-stage or on-market assets across a variety of therapy areas. Table 3 presents the top 10 partnering deals of 2016 as ranked by upfront consideration (including both cash and equity investments). The list does not include settlement deals or product divestments. Surprisingly, oncology does not feature at the top of the list, perhaps due to a dearth of late-stage available assets in this therapy area, driving M&A over licensing.

The largest total upfront consideration was the US$595 M that AbbVie paid Boehringer Ingelheim for global rights to develop and commercialise BI 655066, an anti-IL-23 monoclonal antibody in Phase III development for psoriasis and with potential in the treatment of Crohn's disease, psoriatic arthritis and asthma (Deal no. 70002). With the deal, AbbVie also gained option rights to BI 655064, an anti-CD40 antibody in Phase I development. The agreement represents another attempt by AbbVie to reduce its reliance on Humira® (adalimumab), which accounted for 61% of the company's sales in 2015 but which faces an impending loss of market exclusivity. The furthest advanced adalimumab biosimilar in the US is Amgen's Amjevita™, which was approved by the FDA in September 2016. While Amgen hopes to launch the biosimilar in 2017, in doing so it would risk infringing patents that AbbVie believes are valid until 2022.

The deal between Akebia Therapeutics and Otsuka Pharmaceutical for the co-development and co-commercialisation of vadadustat, an oral hypoxia-inducible factor (HIF) stabiliser in Phase III development for the treatment of anaemia related to chronic kidney disease, is the third-ranked partnering deal taking into account the US$125 M upfront payment, US$35 M in reimbursement for development funding and a further US$105 M contribution to development costs (Deal no. 75648). These committed payments will be much welcomed by Akebia. Vadadustat faces tough competition from HIF-targeting roxadustat, which is in Phase III development by FibroGen in collaboration with Astellas Pharma (Deal no. 24108) and AstraZeneca (Deal no. 53779), and GlaxoSmithKline's oral HIF inhibitor daprodustat, which has also entered Phase III development.

The licence agreement between Exelixis and Ipsen for cabozantinib comes eighth in the top partnering deals list thanks to an upfront payment of US$200 M, but would rank higher if the deal included rights in the US, Canada and Japan (Deal no. 69907). Cabozantinib is marketed as Cometriq® in the US and Europe for the treatment of advanced medullary thyroid cancer and in April 2016 the drug was approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) in patients who have received prior anti-angiogenic therapy. Exelixis had been looking for an ex-US partner for cabozantinib for some time and in Ipsen it secured a collaborator with an established presence in Europe, including in urology-oncology. While the deal was well received from Exelixis' perspective, it was less so on the part of Ipsen, with some analysts regarding the deal terms as onerous. Nevertheless, with the deal, the French company obtained a promising asset for which much of the development risk in RCC had been eradicated.

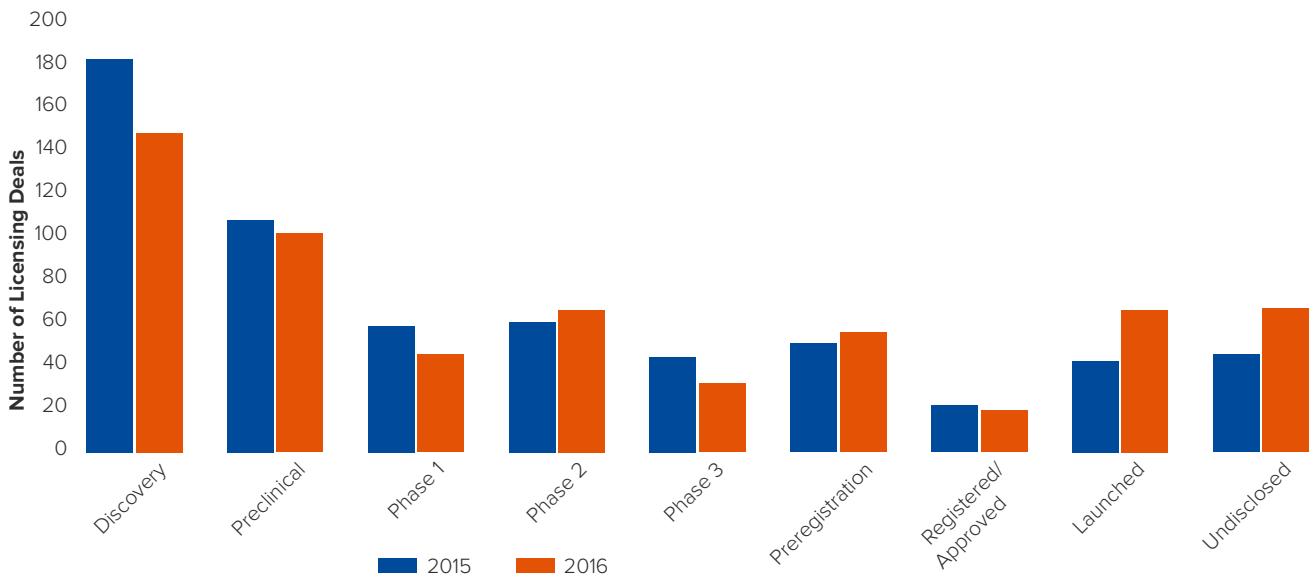
Table 3: Top partnering deals (excluding settlements and product acquisitions) of 2016 by upfront consideration

Total Deal Value	Upfront Payment	Companies	Interest Area	Development Phase
US$595 M	US$595 M	Boehringer Ingelheim, AbbVie	BI 655066, an anti-IL-23 (anti-interleukin-23) monoclonal antibody in Phase III development for psoriasis	Phase III
US$310 M	US$310 M	AstraZeneca, China Medical Systems	Commercialisation rights in China to the calcium channel blocker, Plendil® (felodipine)	Launched
US$1030 M	US$265 M (US$125 M upfront cash, US$105 M in development funding, US$35 M payable at end of Q1 2017)	Akebia Therapeutics, Otsuka Pharmaceutical	Vadadustat, an oral hypoxia-inducible factor (HIF) stabiliser for the treatment of anaemia related to chronic kidney disease	Phase III
US$2561 M	US$261 M (US$22% upfront cash, US$36 M equity)	Jounce Therapeutics, Celgene	JTX-2011, targeting inducible T-cell co-stimulator (ICOS), and up to four early-stage immuno-oncology programmes	Preclinical, Discovery
US$2610 M	US$250 M	Regeneron Pharmaceuticals, Teva Pharmaceutical Industries	Fasinumab, a nerve growth factor (NGF) antibody	Phase IIII (osteoarthritis pain)
US$1520 M	US$250 M	MedImmune/ AstraZeneca, Allergan	MEDI2070, an anti-IL-23 monoclonal antibody in Phase IIb clinical development for moderate-to-severe Crohn's disease	Phase II
US$1054 M	US$200 M	Agios Pharmaceuticals, Celgene	Immuno-oncology therapies based on Agios' cellular metabolism research platform	Discovery
US$855 M	US$200 M	Exelixis, Ipsen	Development and commercialisation of cabozantinib outside the US, Canada and Japan	Launched, Registration pending, Phase III
US$200 M	US$200 M	Moderna Therapeutics, Merck & Co.	messenger RNA (mRNA)-based personalised cancer vaccines	Discovery
US$1775 M	US$175 M	Symphogen, Baxalta	Collaboration to advance immuno-oncology therapeutics against six checkpoint targets	Discovery

Source: IMS PharmaDeals

The volume of licensing deals for therapeutic programmes fell 4% from 2015 to 2016, a smaller decrease than the overall decline in licensing activity in the life sciences sector. Figure 9 presents an analysis of licensing activity for therapeutic programmes in 2015 and 2016 by development stage. Where deals concern multiple assets or assets in different stages of development for different indications, the highest achieved development phase has been selected for the analysis. Licensing at the discovery stage decreased by 17% from 2015 to 2016, in part a consequence of an upturn in option-based deals for discovery-stage programmes from 2015 to 2016. Despite overall licensing activity being in decline, the number of licensing deals for Phase II assets actually increased from 2015 to 2016. The Phase II deals were a mixed bag, including regional deals, deals for specific indications and a number of big pharma out-licensing deals such as GlaxoSmithKline's deal with ZAI Labs for two anti-inflammatory assets (Deal no. 74328), Genentech's agreement with Novogen for the phosphoinositide-3-kinase (PI3K) pathway inhibitor GDC-0084 (Deal no. 74497) and AstraZeneca's deal with Millendo Therapeutics for the polycystic ovary syndrome candidate AZD4901 (Deal no. 69205). More licensing deals were also seen for preregistration and launched products, most of which were regional, single territory or generic deals.

Figure 9: Therapeutic licensing deals by development stage, 2015 vs. 2016



Source: IMS PharmaDeals

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 10). Mean upfront payments for clinical-stage assets increased markedly over the 2012-2015 time period. However, this trend failed to continue in 2016 with mean upfronts for products at all the stages of development analysed, with the exception of Phase III, declining from 2015 to 2016. Most significantly, the mean upfront payments for Phase I and Phase II licensing deals fell by 45% and 58%, respectively, from 2015 to 2016. The largest recorded upfront payment for a Phase I deal in 2016 was the US$125 M that Allergan paid Sosei's Heptares Therapeutics for exclusive global rights to a broad portfolio of subtype-selective muscarinic receptor agonists in development for the

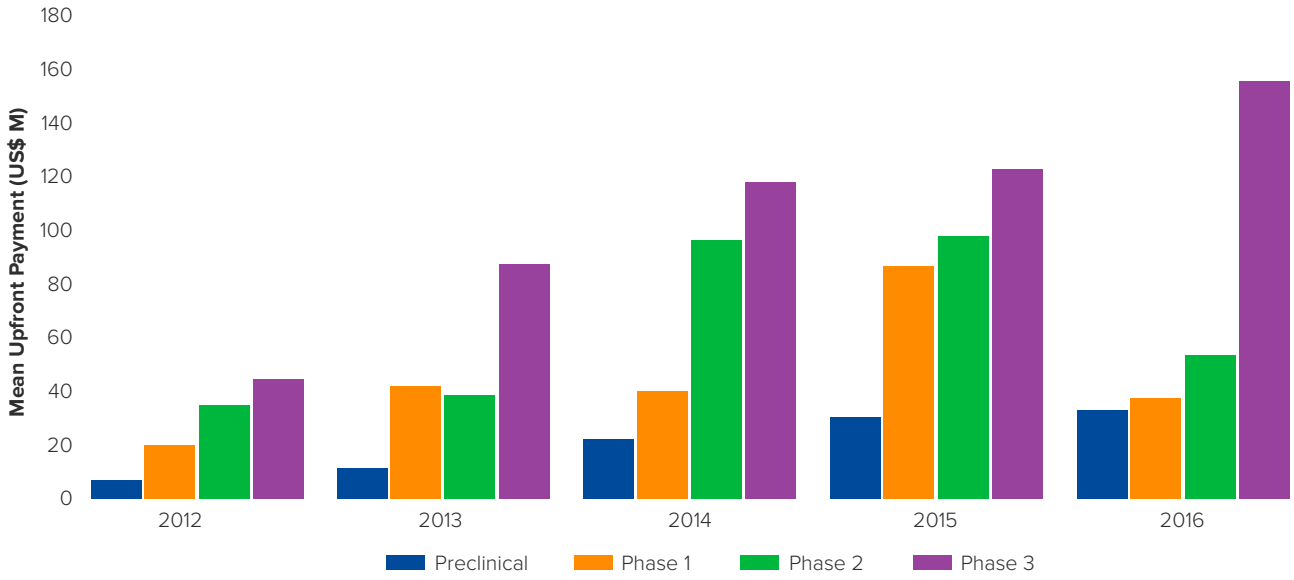
treatment of major neurological disorders, including Alzheimer's disease (Deal no. 70638). In contrast, 2015 saw two record-breaking Phase I immuno-oncology deals with upfront payments in excess of US$300 M: BMS agreed to pay Five Prime Therapeutics US$350 M upfront to license the US biotech's colony stimulating factor 1 receptor (CSF1R) antibody programme (Deal no. 67223); and 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).

The mean upfront payment for Phase III licensing deals in 2016 was US$126.4 M, a 4% increase on 2015 in major part due to the US$595 M upfront of the AbbVie/ Boehringer Ingelheim deal for BI 655066, the largest upfront consideration for a Phase III licensing deal on record. Another significant Phase III deal was the US$250 M upfront partnership between Teva Pharmaceutical Industries and Regeneron to co-develop and commercialise fasinumab (REGN475), an anti-NGF (nerve growth factor) antibody in Phase III development for osteoarthritis pain and Phase II for chronic low back pain (Deal no. 73586). This was regarded as a somewhat risky deal given the safety concerns that have plagued NGF inhibitors. In December 2010, for example, development of the entire class of NGF inhibitors was put on clinical hold by the FDA over safety concerns related to joint destruction. Somewhat ominously, just one month after the Teva/ Regeneron deal was signed, the FDA put a Phase IIb study of fasinumab in chronic low back pain on clinical hold and requested an amendment of the study protocol after observing a case of adjudicated arthropathy in a patient receiving high dose fasinumab who had advanced osteoarthritis at study entry. Based on these results, the two companies plan to design a pivotal Phase III study in chronic low back pain that excludes patients with advanced osteoarthritis.

Big pharma chose more often to out-license than in-license at the Phase II stage in 2016, which only produced one deal with an upfront payment in excess of US$200 M

At the preclinical stage, the largest upfront payment for a single asset licensing deal was the US$75 M that J&J's Janssen Biotech division paid to MacroGenics for global rights to MGD015 (discussed earlier in this review). Big pharma chose more often to out-license than in-license at the Phase II stage in 2016, which only produced one deal with an upfront payment in excess of US$200 M (AstraZeneca's out-licensing deal with Allergan for MEDI2070). In comparison, there were four Phase II deals in 2015 with upfront fees in excess of US$200 M and two deals with upfront payments in excess of US$700 M in 2014.

Figure 10: Mean upfront payment for licensing deals by development stage, 2012-2016



Source: IMS PharmaDeals

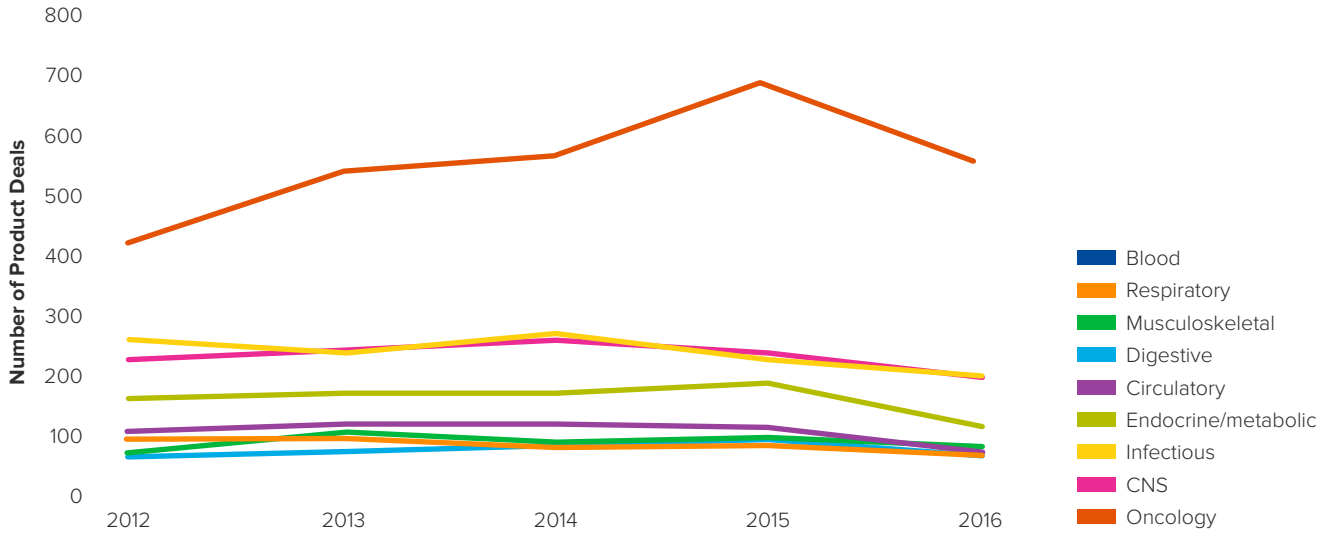
Oncology partnering dampens in line with overall dealmaking decline

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 2016 that were ascribed an indication involving therapeutics, diagnostics or medical devices for cancer. Figure 11 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 2016 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 2016, respectively. While the number of oncology product deals decreased by 18% from 2015 to 2016, the proportion of product deals involving oncology remained in the region of 30%.

Within the oncology field, the most significant activity was in the immuno-oncology sector, with the majority of immuno-oncology deals being early-stage R&D collaborations or option-based deals. Noteworthy alliances include Roche's collaboration with Blueprint Medicines for the discovery, development and commercialisation of up to five small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy (Deal no. 70287) and Baxalta's discovery deals with Symphogen (Deal no. 68832) and Precision BioSciences (Deal no. 69810) for immune checkpoint therapies and allogeneic CAR-T (chimeric antigen receptor T-cell) therapies, respectively.

Almost three times as many product deals in 2016 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.

Figure 11: Number of product deals by therapeutic area, 2012-2016



Source: IMS PharmaDeals

Bristol-Myers Squibb (BMS) was a high-profile immuno-oncology dealmaker, signing a number of deals aimed at expanding the scope of its existing immuno-oncology franchise. In a deal worth up to US$525 M it acquired Cormorant Pharmaceuticals and thereby gained full rights to the company's HuMax®-IL8 antibody programme and its lead candidate HuMax®-IL8, a Phase I/II monoclonal antibody targeted against interleukin-8 that is potentially complementary to T-cell directed antibodies and co-stimulatory molecules (Deal no. 72144). It also licensed global rights to NG-348, a preclinical-stage, armed oncolytic virus with the goal of addressing solid tumours, from PsiOxus Therapeutics for US$50 M upfront (Deal no. 75595), established a research collaboration with Johns Hopkins University focused on unravelling the predictors of response and resistance in patients administered with checkpoint inhibitor-based cancer immunotherapies (Deal no. 75201) and partnered with Enterome Bioscience to identify microbiome-derived biomarkers to improve clinical outcomes for patients treated with its existing immuno-oncology assets using the French start-up's metagenomics platform (Deal no. 74903). As such, it is the first major pharmaceutical company to sign a microbiome deal in the immuno-oncology field. BMS also established multiple clinical trial collaborations in 2016 to test Opdivo® (nivolumab) in combination with oncology assets from various companies, including Calithera Biosciences (Deal no. 75657), Infinity Pharmaceuticals (Deal no. 74754), Nektar Therapeutics (Deal no. 73711), Janssen Biotech (Deal no. 72428) and AbbVie (Deal no. 72441).

There was some noteworthy deal activity in the CNS field in 2016. In November, Allergan acquired Chase Pharmaceuticals for US$125 M upfront, with the potential for a total consideration of US$1 B subject to the achievement of certain milestones payments, and thereby gained CPC-201, a patent-protected combination of donepezil and solifenacin that will be advanced into a Phase III study in Alzheimer's disease in 2017 (Deal no. 75048). A few weeks earlier, Sumitomo Dainippon Pharma's Sunovion Pharmaceuticals acquired Canadian biotech Cynapsus Therapeutics for approximately US$624 M in cash (Deal no. 73189).

The key driver of the acquisition was Cynapsus' Phase III candidate APL-130277, a sublingual thin film reformulation of the dopamine agonist apomorphine that is designed to be a fast-acting and on-demand treatment option for managing the debilitating 'OFF' episodes associated with Parkinson's disease (PD). It offers a more convenient mode of administration and an improved side-effect profile compared to subcutaneously delivered apomorphine.

Companies developing therapeutics for the treatment of NASH were attractive takeover targets in 2016. Gilead Sciences acquired Nimbus Apollo, a wholly owned subsidiary of Nimbus Therapeutics, and its acetyl-CoA carboxylase (ACC) inhibitor programme for US$400 M upfront and up to US$800 M in development-related milestones (Deal no. 70562). The deal, which failed to impress investors, gave Gilead full rights to develop and commercialise NDI-010976, which has since entered Phase II development, as well as other preclinical ACC inhibitors for the treatment of NASH and for the potential treatment of hepatocellular carcinoma. Allergan's acquisitions of Tobira and Akarna, discussed earlier in this review, intensified interest in the field. NASH represents a therapy area characterised by high unmet medical need and other deals in 2016 centred on drug candidates for the disease include the merger of Synta Pharmaceuticals and Madrigal Pharmaceuticals (Deal no. 72217) and Tobira's licensing deal with Dong-A ST for exclusive rights to develop and market Suganon® evogliptin in combination with cenicriviroc, and as a single agent, in the US, Canada, Europe and Australia for NASH (Deal no. 70826). Moreover, in December and in return for a US$50 M fee, Conatus Pharmaceuticals granted Novartis an option to license the orally active pan-caspase inhibitor emricasan, which is being evaluated in a Phase IIb trial for NASH fibrosis (Deal no. 75598).

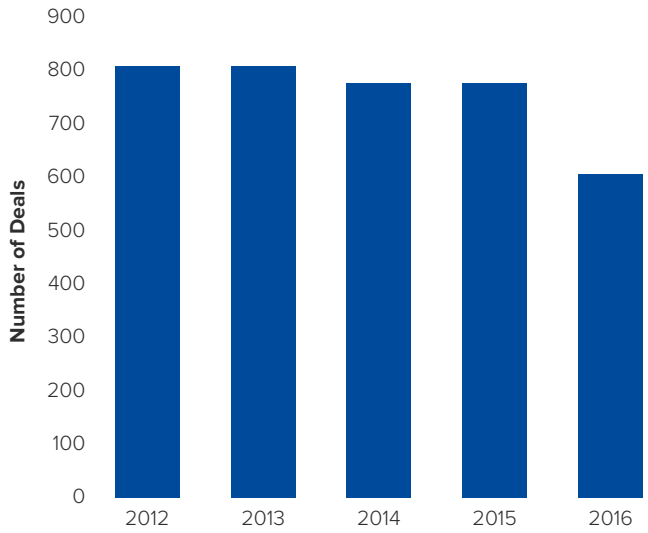
Multiple programmes drive higher upfront payments for R&D alliances

Outpacing the overall decline in dealmaking in the life sciences sector, notably fewer collaborative R&D deals (defined here as discovery or preclinical-stage deals where the companies involved are actively collaborating on research and development) were entered into in 2016 compared with previous years (Figure 12). Indeed, the level of collaborative R&D dealmaking, which peaked in 2013, fell by 22% from 2015 to 2016. 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) reached its highest level in 2015, reaching an unprecedented US$36.9 B, more than double the cumulative value of the collaborative R&D deals signed in 2012 (Figure 13). The upward trajectory failed to continue in 2016, however, with the aggregate total deal value for collaborative R&D deals falling 32% to US$25.2 B. In spite of this, the mean total deal value, excluding royalties, of those collaborative R&D deals with disclosed financial terms rose by 17% in 2016 to US$561 M, with eight deals having a headline value in excess of US$1 B. Therefore, although fewer collaborative R&D deals were signed in 2016, on average they were of higher total potential deal value. In most cases, these high potential deal values were driven by the inclusion of multiple targets or programmes in the collaboration and as such are unlikely to be realised.

–22%

The level of collaborative R&D dealmaking, which peaked in 2013, fell by 22% from 2015 to 2016.

Figure 12: Number of collaborative R&D deals, 2012-2016



Source: IMS PharmaDeals

Because collaborative R&D deals are typically heavily backloaded in their deal structures, it is often more meaningful to consider trends in the upfront payments for such deals. In parallel with the rise in the mean total deal value, the mean upfront payment for collaborative R&D deals rose by 13% from 2015 to 2016 to reach US$39.4 M, with four such deals having upfront payments exceeding US$100 M (Figure 14). Interestingly, all four of these deals were broad alliances in the highly competitive immuno-oncology field, which is seeing a land grab for next-generation assets. The observed upward shift in upfront payments for R&D collaborations likely reflects fierce competition for these and other attractive early-stage assets amongst biopharmaceutical companies keen to secure the long-term growth prospects of key franchises.

Merck & Co. deepened its relationship with Moderna Therapeutics in June 2016 with a collaboration and licence agreement to develop and commercialise mRNA-based personalised cancer vaccines (Deal no. 72186). Merck paid Moderna US$200 M upfront, which Moderna will use to lead all R&D efforts through proof-of-concept and to fund a portion of the build-out of a GMP manufacturing facility. The development programme will entail multiple studies in several types of cancer and include the evaluation of mRNA-based personalised cancer vaccines in combination with Merck's Keytruda. With the deal, Merck is hoping that combining immunotherapy with vaccine technology will improve outcomes for cancer patients and thus the commercial reach of Keytruda. In another example of a company expanding a collaboration with a long-standing partner, in May 2016 Celgene paid Agios Pharmaceuticals US$200 M upfront in return for opt-in rights to co-develop and co-commercialise metabolic immuno-oncology therapies based on Agios' cellular metabolism research platform (Deal no. 71369). Metabolic immuno-oncology is an emerging field of cancer research focused on altering the metabolic state of immune cells to enhance the body's immune response to cancer.

Table 4 presents the top 10 collaborative R&D deals of 2016 as ranked by total potential deal value. Unsurprisingly, immuno-oncology features heavily on the list. It is also interesting to note that the majority of the deals relate to biological therapies, with bispecific antibodies, gene therapies, cell therapies, RNA-based therapeutics and engineered peptides all included.

The three largest collaborative R&D deals of 2016 have headline values in excess of US$2 B but closer inspection reveals that they pertain to a large number of programmes. Incyte's deal with Dutch biotech Merus for the research, discovery and development of bispecific antibodies utilising Merus' Bioclonics® technology platform is the largest collaborative R&D deal in terms of biodollars but its position at the top of the list reflects the fact that it involves up to 11 research programmes, including two of Merus' preclinical immuno-oncology programmes (Deal no. 75621). Although, at US$120 M, the upfront consideration is certainly sizeable and Incyte will take a US$80 M equity investment in Merus, total milestone payments are only US$350 M per programme for those programmes that are not the subject of co-development and co-commercialisation.

Figure 13: Aggregate value and mean total deal value of collaborative R&D deals, 2012-2016

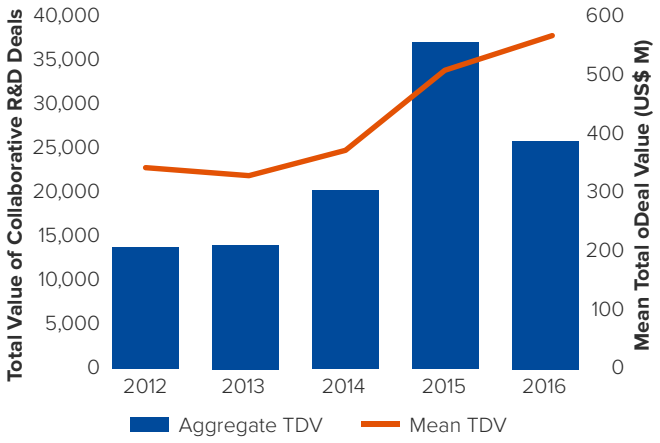
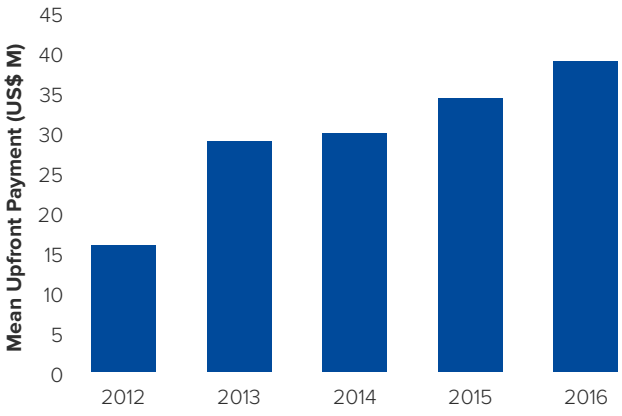


Figure 14: Mean upfront payment for collaborative R&D deals, 2012-2016



Source: IMS PharmaDeals

Table 4: Top therapeutic collaborative R&D deals of 2016 by total potential deal value

Total Deal Value	Upfront Payment	Companies	Interest Area	No. of Targets/ Programmes
US$3000 M	US$120 M	Merus, Incyte	Bispecific antibodies, including two preclinical immuno-oncology programmes	11 (Preclinical, Discovery)
US$2258 M	Undisclosed	DiCE Molecules, Sanofi	New oral therapeutics for up to 12 targets using DiCE's directed chemical evolution discovery platform	12 (Discovery)
US$2000 M	US$20 M	University of Pennsylvania, Biogen	Collaboration to advance gene therapy and gene editing technologies, targeting the eye, skeletal muscle and CNS	7 (Preclinical, Discovery)
US$1705 M	US$105 M	Precision BioSciences, Baxalta	Allogeneic chimeric antigen receptor (CAR) T-cell therapies directed towards areas of major unmet need in multiple cancers	6 (Discovery)
US$1144.5 M	US$5 M	Cerulean Pharma, Novartis	Nanoparticle-drug conjugates combining Cerulean's Dynamic Tumor Targeting™ technology with Novartis' compounds	5 (Preclinical)
US$1054 M	US$200 M	Agios Pharmaceuticals, Celgene	Immuno-oncology therapies based on Agios' cellular metabolism research platform	Multiple (Discovery)
US$1015 M	US$15 M	Medigene, Bluebird bio	T-cell receptor (TCR) immunotherapies	4 (Discovery)
US$1000 M	Undisclosed	Bicycle Therapeutics, AstraZeneca	Bicyclic peptides (Bicycles®) for the treatment of respiratory, cardiovascular and metabolic diseases	Undisclosed (Discovery)
US$911 M	US$40 M (US$10 M cash + US$30 M equity investment)	Wave Life Sciences, Pfizer	Nucleic acid therapies aimed at silencing the underlying causes of debilitating metabolic diseases	5 (Discovery)
US$790 M	US$36 M (upfront fee, investment, research funding + preclinical milestones)	Crescendo Biologics, Takeda Pharmaceutical	Humabody® -based therapeutics for cancer indications with a high unmet medical need	Multiple (Discovery)

Source: IMS PharmaDeals

Merus retains US rights to one preclinical programme and has the option to co-fund development of product candidates arising from two other programmes. The deal is an impressive achievement for Merus, which counts Novartis, J&J and Pfizer among its investors, and which retains rights to its lead drug candidate MCLA-128, which is currently in Phase I/II development for various solid tumour indications.

Continuing its strategy of investing in early-stage start-ups as part of its Sunrise Initiative, in March 2016 Sanofi entered into a 5-year collaboration with Stanford University spin-out DiCE Molecules to discover potential new oral therapies for up to 12 targets spanning disease areas of strategic interest to Sanofi (Deal no. 70179). DiCE's small molecule discovery platform has the potential to develop compounds that act by unlocking protein-protein interfaces, which have historically been regarded as intractable targets for orally bioavailable drugs. According to the deal terms, Sanofi will provide funding in excess of US$50 M in equity, upfront, target exclusivity, technology access fees and research services. In addition, DiCE is eligible to receive up to US$184 M in research, clinical and regulatory milestone payments per target, plus royalties, bringing the total potential deal value to US$2.26 B. In January 2016, Sanofi reshaped its collaboration with Warp Drive Bio with a US$750 M alliance to discover cancer therapies targeting human oncogenes and antibiotics targeting Gram-negative bacteria utilising Warp Drive's SMART™ (small molecule assisted receptor targeting) and genome mining platforms (Deal no. 68941). The French company ended the year partnering with Taiwan's JHL Biotech for the development and commercialisation of biosimilars in China, with potential international expansion, in a US$337 M deal (Deal no. 75281).

It must be noted that the collaborative R&D deal dataset does not include deals where a company has been granted an option to license discovery or preclinical-stage programmes at a defined future point in development and which involve no collaboration on R&D prior to option exercise. Many big pharma and biotech companies took advantage of such deal structures in 2016 (Table 5). The largest upfront consideration for a discovery or preclinical-stage option deal was the rather bold US$225 M that Celgene agreed to pay 3-year-old biotech start-up Jounce Therapeutics to obtain options on Jounce's lead product JTX-2011, which has since entered clinical development, and up to four undisclosed early-stage immuno-oncology programmes to be selected from a defined pool of B-cell, T-regulatory cell and tumour-associated macrophage targets derived from the company's translational science platform (Deal no. 72413). In addition, Celgene has been granted an option for 50% ownership of a checkpoint programme, JTX-4014. The deal also includes a US$36 M equity investment from Celgene, payments on achieving regulatory, development and net sales milestones that could amount to US$2.3 B in total across all programmes reaching commercialisation, and tiered royalties on ex-US sales. The US$225 M upfront payment, one of the largest recorded in the IMS PharmaDeals database for a preclinical-stage immuno-oncology partnering deal, was an astounding endorsement for Jounce, which was only launched by Third Rock Ventures in 2013 and which at the time of the deal had only raised a little more than US$100 M. For Celgene it demonstrated once again that the company is willing to pay handsomely to secure access to high-risk but potentially high-reward assets at a very early stage of development.

One of the largest collaborative R&D deals of 2016 in terms of headline value was Biogen's potential US$2 B agreement to leverage research from the Gene Therapy Program at the University of Pennsylvania (UPenn) in order to develop treatments for ocular, skeletal muscle and CNS disorders using adeno-associated virus (AAV) gene delivery vectors (Deal no. 71323).

Under the terms of the agreement, Biogen has the option to rights to UPenn's next-generation AAV vectors and in return the university receives US$20 M upfront plus US$62.5 M in R&D funding, with a minimum of US$77.5 M in milestone payments per programme plus royalties. In the same month, Biogen also entered into a research alliance with UPenn spin-off Regenxbio for the development of gene therapy product candidates based on the NAV® technology platform for the treatment of two rare vision disorders (Deal no. 71331). The deals came nearly 1 year after Biogen's US$1.2 B collaboration with Applied Genetic Technologies to develop gene therapies in ophthalmology (Deal no. 65468).

Table 5: Selected option deals

Total Deal Value	Upfront Payment	Companies	Interest Area	No. of Targets/ Programmes
US$2561 M	US$225 M	Jounce Therapeutics, Celgene	Next-generation immuno-oncology therapies, including preclinical-stage JTX-2011, targeting ICOS (inducible T-cell co-stimulator)	6 (Preclinical, Discovery)
US$1775 M	US$175 M	Symphogen, Baxalta	Immuno-oncology therapeutics against six checkpoint targets	6 (Discovery)
US$1010 M	US$45 M	Blueprint Medicines, Roche	Small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy	5 (Discovery)
US$790 M	Undisclosed	Exicure, Purdue Pharma	Treatments for psoriasis and other diseases amenable to a gene regulation approach utilising Exicure's SNA(TM) (spherical nucleic acid) technology	4 (Phase I, Discovery)
US$750 M	Undisclosed	C4 Therapeutics, Roche	Small molecule targeted protein degradation (TPD) therapeutics	Undisclosed (Discovery)
US$722 M	US$50 M	Conatus Pharmaceuticals, Novartis	Orally active pan-caspase inhibitor emricasan for liver cirrhosis and liver fibrosis	1 (Phase II)
US$685 M	US$40 M	arGEN-X, AbbVie	ARGX-115, a preclinical-stage human antibody programme targeting the novel immuno-oncology target GARP	>1 (Preclinical)
US$619 M	US$1 M	Redwood Bioscience, Roche	Next-generation molecules coupling different therapeutic modalities using Catalent's SMARTag™ technology	Undisclosed (Discovery)

Source: IMS PharmaDeals

Another high-value gene therapy deal in 2016 was Spark Therapeutics' licensing agreement with Selecta Biosciences, which gave Spark exclusive worldwide rights to Selecta's proprietary Synthetic Vaccine Particles (SVP™) platform technology for co-administration with gene therapy targets, including FVIII for haemophilia A, as well as exclusive options for up to four additional undisclosed genetic targets (Deal no. 75382). The deal is potentially worth more than US$2.1 B, although the upfront consideration is very modest (US$10 cash upfront payment, US$5 M equity investment).

Orphan drugs remain important deal drivers

22 novel drugs were approved by the FDA's Center for Drug Evaluation and Research (CDER) in 2016, nine of which were approved to treat rare diseases affecting 200,000 or fewer Americans. In comparison, there were 45 novels drug approvals in 2015 (21 of which were for rare diseases) and from 2007 through 2015 the CDER has averaged about 30 novel drug approvals per year. Orphan drugs continued to drive significant deal activity in 2016, involving big pharma and speciality pharma companies.

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In order to gain an orphan asset with near-term revenue potential and help diversify its business away from the narcolepsy drug Xyrem® (sodium oxybate), in May 2016 Jazz Pharmaceuticals agreed to pay a 73% premium to acquire Celator Pharmaceuticals for approximately US$1.5 B in cash (Deal no. 71667). The key driver of the deal was Vyxeos™ (cytarabine:daunorubicin), an optimised encapsulated formulation of two existing chemotherapy drugs developed using Celator's CombiPlex® platform that prolonged the life of elderly patients with secondary acute myeloid leukaemia by 3.61 months versus the standard of care in a Phase III trial. Following the controversial FDA approval of its Duchenne muscular dystrophy (DMD) drug Exondys 51™ (eteplirsen), in October Sarepta Therapeutics signed a deal potentially worth more than US$950 M in order to gain rights in the EU, Switzerland, Norway, Iceland, Turkey and the CIS to Summit Therapeutics' utrophin modulator pipeline, including its clinical DMD candidate ezutromid (Deal no. 73945). Signalling its intention to focus on the orphan drug space, in October 2016 Horizon Pharma acquired rare disease specialist Raptor Pharmaceuticals in a deal worth approximately US$800 M (Deal no. 73435). The acquisition diversified the company's growing orphan drug business with the addition of Procysbi® (cysteamine bitartrate delayed-release) and Quinsair™ (levofloxacin), which are approved for nephropathic cystinosis and chronic pulmonary infection in cystic fibrosis, respectively. The deal also increased Horizon's geographic footprint and reduced its dependence on the primary care market.

Pfizer strengthened its orphan drug portfolio and significantly expanded its expertise in the gene therapy field in August 2016 by acquiring the 78% of privately held US biotech Bamboo Therapeutics that it did not already own for US$150 M upfront plus the potential for up to US$495 M in contingent milestones (Deal no. 72653). Bamboo is focused on developing gene therapies for the potential treatment of patients with certain rare diseases related to neuromuscular conditions and those affecting the CNS. Pfizer had bought a 22% ownership position in Bamboo for US$43 M earlier in 2016. With the acquisition, it gained a Phase I/II and three preclinical-stage gene therapies for neurological and neuromuscular conditions, along with a manufacturing facility. In November, Novartis exercised an option granted to it in 2012 to acquire privately held Selexys Pharmaceuticals following the receipt of positive results from a Phase II study of Selexys' lead asset SelG1 (SEG101, crizanlizumab) in patients with sickle cell disease (Deal no. 48676). The deal is potentially worth up to US$665 M in upfront, acquisition and milestone payments.

Outlook for 2017

Biopharmaceutical companies exercised caution in their dealmaking activities in the latter part of 2016 following the Brexit vote and ahead of the US presidential election. The threat of drug price reform remains a particularly critical issue for the pharmaceutical industry and, despite an initially positive response to the US presidential election result, huge uncertainty surrounds the impact of the Trump administration on the sector, with the new president having promised to lower drug prices and repeal the Affordable Care Act. Until the economic and political uncertainty currently facing the pharmaceutical industry is resolved, we can expect overall deal volumes to be depressed compared to previous years.

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M&A was generally subdued in the life sciences sector in 2016, with limited big pharma participation beyond a few asset-driven acquisitions. The first quarter of 2017, however, has already seen some significant M&A activity such as Takeda's US$5.2 B deal to buy Ariad Pharmaceuticals (Deal no. 76052) and J&J's US$30 B buyout of Actelion (Deal no. 76351). Both companies had been regarded as likely takeover targets for some time and it remains to be seen whether or not these very high premium deals will mark the start of an upturn in the level of consolidation in the life sciences sector. Donald Trump has indicated that the US will become business friendly under his leadership and a repatriation holiday, which would allow US companies to access cash held overseas without incurring significant tax penalties, is a distinct possibility. This could fuel significant deal activity in the biopharmaceutical sector should it go ahead, particularly for companies facing slow sales growth or pipeline deficiencies.

Partnering activity in the life sciences sector will continue at a steady pace in 2017, but it is unlikely to reach the levels seen in previous years. The sharp drop in new drug approvals in 2016 highlights the issue of declining R&D productivity that continues to plague the industry. As the blockbuster model increasingly looks like a relic of the past, big pharma is now relying on products targeting smaller patient populations to drive growth. The need for new sources of innovation is ever present. Orphan drug and immuno-oncology deals will therefore continue to be prevalent, as will deals giving access to novel technology platforms or therapeutic modalities. Straight licensing deals may decline in popularity in favour of creatively structured option-based deals that mitigate the risk of accessing innovation at a very early development stage but which offer long-term upside for the biotech drug developers.

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