Building for big pharma

Asiya Giniatullina, Marco Boorsma, Geert-Jan Mulder & Sander van Deventer

With acquisition the most likely exit for today's biotech investors, it pays to keep current with the tastes of pharmaceutical firms when launching a venture.

Large-scale mergers and acquisitions (M&A) activity is an integral pipeline expansion strategy of the pharmaceutical industry and will contribute nearly two-thirds of sales growth over 1995–2014[1]. This is in line with the recent pharmaceutical trends of reducing internal R&D and increasing the in-licensing of early clinical stage drug candidates. This trend is dovetailing with a stern public market, which is preventing all but select life science companies from joining its ranks. Together, this means that most biotech companies today are being built with an acquisition in mind as the preferred exit for initial investors.

At Forbion, pharmaceutical purchase is often the end game for the companies we build, so we keenly track big pharma's areas of interest as it helps us envision how we will eventually leave our investment. However, information on the movements of big pharma is also valuable for the business development of small startups and to bioentrepreneurs because pharmaceutical companies will often be your source of income through partnering, as well as frequently being the exit that gives your initial investors a return.

Thus, the question is how do you find out what interests big pharma? Most companies make their target partnering areas known through dedicated sections on their websites and in brochures describing business development interests. This information can range from global descriptions of therapeutic areas into which expansion of product offerings is desired to very detailed data about diseases, classes of molecules and pathways sought after. They even sometimes specify areas of *no* interest.

We wanted to know if big pharma can be taken at its word, so we analyzed the deals executed by pharmaceutical companies during the past seven years and identified the most popular areas for acquisition and licensing. Additionally, we analyzed the values of the transactions by therapeutic area and development phase of the lead product to better understand what big pharma is willing to pay and when (**Box 1**). Finally, we correlated these areas of declared interest with actual pharmaceutical acquisitions in order to validate the consistency of their indications with actual M&A activity. What emerges is a modern map of big pharma wants and pay scales that bioentrepreneurs should consult before beginning their life as a founder or with a startup.

Partnering interest

We compiled a list of 33 large and mid-sized pharmaceutical and biotech companies that are typical acquirers of venture-backed, early stage companies. Of these, 27 publically indicated their partnering interests by therapeutic area, which we marked and standardized by defining therapeutic areas based on World Health Organization (WHO) classification (http://apps.who.int/classifications/icd10/browse/2010/en). (We added two areas not on the main WHO list—chronic inflammation and women's health—and we also recorded any declared interest in platform technologies.) Each company indicated 1–11 areas of interest, with an average of 5.7 (median of 6). The most popular areas of partnering interest were CNS, chronic inflammation and oncology (**Fig 1**; big pharma–specific interest in **Table 1**; full listings in **Supplementary Table 1**).

We were then able to stratify the data within each therapeutic area for 23 of the 27 companies. Within the CNS category, neurodegeneration (including Alzheimer's disease and Parkinson's disease) and pain were most frequently requested, followed by psychiatric indications (mainly schizophrenia). In oncology, hematologic cancer was most frequently mentioned, followed by gastrointestinal tract, and then prostate, lung and pancreatic indications third. In the chronic inflammation area, rheumatoid arthritis was most frequently mentioned, followed by multiple sclerosis and finally inflammatory bowel disease. Endocrine and metabolic disorders were dominated by diabetes, followed by obesity and lastly fertility. For cardiovascular disease, atrial fibrillation and dyslipidemia topped the list, followed by

Box 1 Big pharma supply and demand

As big pharma's pipeline needs have become dire, it has been willing to pay more for acquisitions. Indeed, the number and volume of acquisitions of biotech companies with upfront payments above $100 million has increased substantially in 2008–2011 (ref. 4). The HBM Partners mergers and acquisitions (M&A) report (http://www.hbmpartners.com/en/about-hbm-partners/report-hbm-partners.php), which also takes into account small-volume acquisitions, shows that after the 2008–2009 dip in buyouts, the number and volume of M&A deals peaked in 2010 but decreased only slightly in 2011. That was followed by the number of therapeutic biotech acquisitions jumping 22% from 2011 to 2012 (ref. 5) and the number of life science M&A deals with values of more than $500 million increasing by 38% (http://www.currentpartnering.com/scorecard/ma/).

Asiya Giniatullina is analyst, Marco Boorsma is principal and Geert-Jan Mulder is general partner at Forbion Capital Partners, Naarden, The Netherlands. Sander van Deventer is general partner at Forbion Capital Partners and professor in the Department of Gastroenterology, Leiden University Medical Center, Leiden, The Netherlands.
e-mail: sander.van.deventer@forbion.com

Table 1 Big pharma partnering interest by therapeutic area

Company	Cardiovascular diseases	CNS	Oncology	Endocrine and metabolic diseases	Infectious diseases	Genitourinary diseases	Blood disorders	Injury	Respiratory diseases	Digestive diseases	Musculoskeletal diseases	Ophthalmology	Ear, nose and throat	Chronic inflammation	Dermatology	Women's health	Congenital diseases	Platforms
Abbott	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Maybe	No	Yes	No	Yes	No	No	No	No
AstraZeneca	Yes	Yes	Yes	Yes	Yes	No	No	Maybe	Yes	Yes	No	Maybe	No	Yes	Maybe	No	No	Yes
Bayer	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	Yes	No	No
Boehringer Ingelheim	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No
Bristol-Myers Squibb	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No
Eli Lilly	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	Maybe
GlaxoSmithKline	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes
Johnson & Johnson	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
Merck	Yes	Yes	Yes	Yes	Yes	Maybe	No	No	Yes	No	No	No	No	Yes	No	No	No	Yes
Novartis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	No	No	No
Pfizer	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Maybe	Yes
Roche	No	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes
Sanofi	No	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	No	Yes	No	No	No	No

The companies we analyzed were: Abbott, Actelion, Alkermes, Amgen, Astellas, Astra Zeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cubist, Daiichi Sankyo, Eli Lilly, Genentech, Gilead, GlaxoSmithKline, Johnson & Johnson, MedImmune, Merck & Co., Merck Serono, Nektar, Novartis, Novo Nordisk, OSI, PDL, Pfizer, Roche, Sanofi, Shire, Takeda, Teva, UCB and Vertex. Seven of them had no partnering information on their websites (Celgene, Cubist, Gilead, Nektar, OSI, PDL and Vertex) and thus were excluded from further analysis. For full list see **Supplementary Table1**.

Source: Company websites, brochures.

heart failure (both acute and chronic). The infectious diseases most frequently mentioned were hepatitis B and C, then HIV and respiratory infections.

Acquisitions analysis

Expressing interest is one thing, but following through is another. To see if big pharma actually bought firms in the areas it suggested, we analyzed the acquisitions of venture-backed life science companies. Commonly these companies have one or two products in the pipeline, and by using the lead compound the firm can be classified by therapeutic area (when multiple therapeutic areas were targeted, we labeled the company 'mixed'). We used the HBM Partners M&A report (http://www.hbmpartners.com/en/about-hbm-partners/report-hbm-partners.php) to obtain the list of acquisitions by the selected 27 companies and tracked 74 acquisitions, for which 68 deal values were known (**Table 2**).

The largest number of acquisitions was in oncology, though the total deal value was relatively low. Although CNS is the number-one partnering interest, with more than 90% of pharmaceutical companies interested in acquiring assets in the CNS space (**Fig. 1**), it was one of the least popular areas for acquisition, possibly because it is generally accepted that drug development in CNS indications is plagued by a high failure rate and CNS drugs take longer to reach approval than any other indication[2].

However, there is a secondary scenario that might be in play: big pharma explores its CNS desires through licensing. To consider this, we searched partnering deals in Europe and North America and found that the number of neurology products out-licensed for develop-

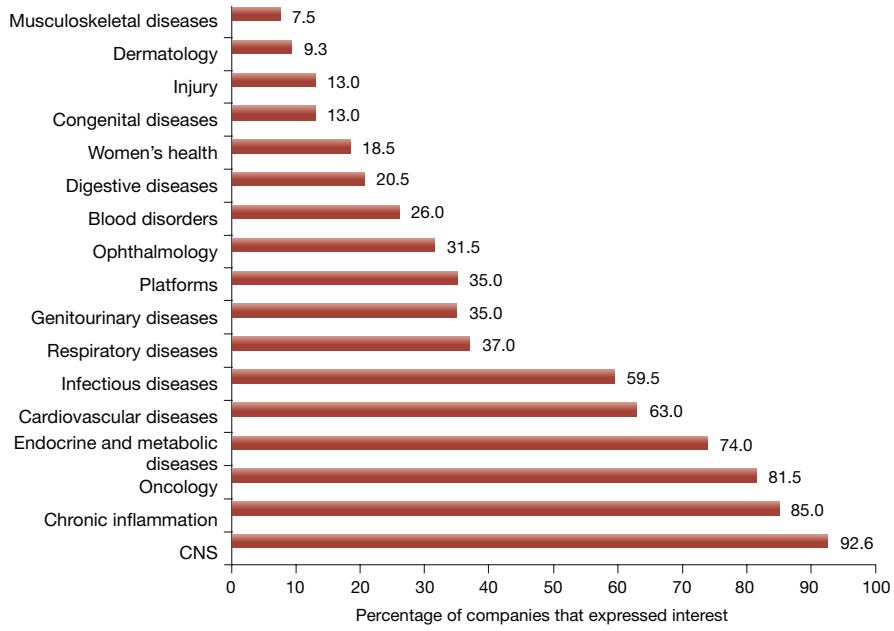

Figure 1 Indicated therapeutic areas of partnering interest for 27 pharmaceutical companies. Information from **Table 1** was quantified by assigning 1 point for Yes, 0.5 for Maybe and 0 for No in each therapeutic area, and then expressed as percentage of all considered companies. Source: company literature and websites as of July 2012. For full list see **Supplementary Table1**.

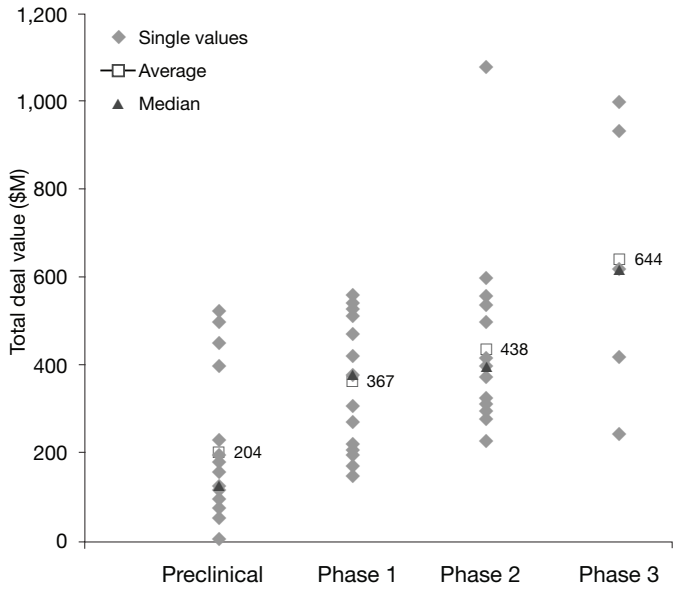

Figure 2 Price distributions by phase of development at acquisition announcement for venture-backed companies from 2005 to mid-2012. (Not all development stages were known; we did not include the few companies that, at the moment of acquisition, had a product on the market.) Source: HBM Partners mergers and acquisitions report 2012.

ment was second highest, as was the number of companies that out-licensed CNS products (**Table 3**). This indicates that CNS assets are in-licensed instead of acquired, allowing for a mitigation of risk through a milestone-based payout model.

To gauge a buyout's value against the target's development stage, we then analyzed M&A deals by stage of development at signing (**Fig. 2**). As expected, phase of development correlated with total deal value, although with a small difference between value of assets in phase 1 and phase 2. This is not surprising—the more developed a product is, the more it has been derisked, and thus it is more valuable to pharma.

Of these 27 pharmaceutical firms, the most active acquirers between 2005 and mid-2012 were Pfizer, which purchased 10 venture capitalist (VC)-backed companies; Amgen with 6; and AstraZeneca, Johnson & Johnson, Merck and Roche with 4 apiece. Each of these companies has established corporate venture divisions, which generally claim a strategic investment focus (for example, investments in companies that develop assets of interest to the pharmaceutical division), and of the 72 acquired companies we looked at, 17 were supported by corporate venture funds. This would suggest a connection between corporate venture investing and eventual acquisition, but only one company, Avidia, was acquired by the pharmaceutical company related to the initial corporate VC investment arm. Although earlier research has shown that involvement of a corporate VC generally generated better returns (see earlier hyperlink to HBM Partners report), it seems that an existing R&D collaboration between a pharmaceutical and biotech company is a better predictor of future acquisition.

Consistency check

For each acquisition, we verified whether it was in line with the partnering interest announced by the buying company. We found that only 5 of the 75 acquisitions we analyzed had a lead product in an area not listed as an interest by the acquirer (**Table 4**), and two of those were in lung fibrosis—an area, along with regenerative medicine, that is growing, because of both population demographics (including aging) and the significant unmet medical needs in these therapeutic areas. This rising interest can be somewhat confirmed by the recent acquisition of Advanced BioHealing for $750 million by Shire.

These five acquisitions outside declared interests are a small sample, but they provide an interesting data point on value. The average total deal value for the companies acquired outside declared big pharma interests was $364 million, whereas it was $479 million for all analyzed acquisitions. This is a subtle reminder that if you are negotiating with a pharmaceutical buyer in an area it has suggested is not its focus, you will have little power to push on price.

Deal values and structured deals

The areas in which total deal value was significantly higher than average came in infectious diseases and the mixed category. Lowest values were associated with platform deals and blood disorders.

A significant number of companies in preclinical development were acquired for between $400 million and $600 million, and two phase 3 companies were acquired for less than $450 million. Surprisingly, when deals were structured (a portion paid up front, with additional consideration for achieving milestones), the development stage did not seem to influence the upfront-to–earn out ratio: for all phases the upfront was roughly half of the total deal value. Also, 75% (12 of 16) of the preclinical stage companies and 83% (5 of 6) of market stage companies were acquired in all-upfront deals.

For phase 2 and phase 3 deals, about 60% (12 of 20 and 4 of 7, respectively) were acquired with all-upfront payments. Only in phase 1 did the majority (73%, 11 of 15) of the deals have

Table 2 Mergers and acquisitions deal statistics for complete acquisition deals realized between January 2005 and June 2012

Therapeutic area	Total spent ($M)	Average total deal value ($M)	Number of deals
Oncology[a]	6,576	387	18
Infectious diseases	6,432	643	10
Mixed	2,470	618	4
Cardiovascular diseases	3,367	561	6
Chronic inflammation	3,339	477	7
Injury[a]	1,787	596	4
Endocrine and metabolic diseases	1,710	428	4
Ophthalmology	1,067	534	2
Platforms[a]	1,526	218	8
CNS[b]	715	358	4
Genitourinary diseases	745	373	2
Respiratory diseases[a]	540	270	3
Blood disorders	445	223	2

[a]Contains one deal of undisclosed value. [b]Contains two deals of undisclosed value.

Source: HBM Partners M&A Report.

Table 3 Licensing deals by therapeutic area

Therapeutic area	Number of products partnered for development	Number of companies that out-licensed products
Oncology	308	164
Neurology	241	140
Infectious diseases	173	94
Endocrine and metabolic diseases	130	83
Cardiovascular diseases	72	53
Dermatology	32	29
Genitourinary diseases	26	26

Source: BCIQ: BioCentury Online Intelligence.

Table 4 Acquisitions completed between 2005 and mid-2012 that were not in line with the partnering interest announced by the buyer company

Buyer	Therapeutic area	Target company	Total deal value ($M)
Bayer	Platforms	Direvo	300
Biogen Idec	Oncology	Conforma	250
	Respiratory diseases/injury	Stromedix	562
Bristol-Myers Squibb	Respiratory diseases/injury	Amira	475
Johnson & Johnson	Drug formulation platform	TransForm Pharmaceuticals	230

Source: HBM Partners M&A Report.

an earn out. When we sorted the number of all-upfront and structured deals by the year when the deal took place, it became obvious that the number of structured deals as compared to all-upfront deals has been growing over the last years, which is not news[4]. Thus, the number of structured deals is rather dependent on the time when the deals were closed rather than development stage. These numbers support the more risk-sharing approach that pharma is currently taking to prevent write-offs in case a technology or compound does not prove its value in advanced development. However, it is remarkable that the upfront paid was half of the total deal value for all phases of development and not significantly lower in the preclinical stage deals.

As big pharma is taking fewer risks these days, entrepreneurs and investors need to be prepared for structured deals in which only part of the total value is paid up front. However, promising biotech assets and companies are still attractive to big pharma—this is evidenced by the continuous M&A activity, significant deal values and big pharma's proactive approach toward biotech companies. Investing or founding companies that develop products in one of the most popular areas for partnering (**Table 2**)—neurology, chronic inflammation, oncology, endocrine and metabolic diseases, cardiovascular disorders and infectious diseases—increases the chance of the company benefitting from meaningful partnerships with a pharmaceutical company, and it also should better the odds of finding an exit with big pharma. Pharmaceutical companies appear to be accessing their most highly desired areas fairly evenly through acquisitions and licensing deals—and both will help your company. But because we are VC investors, we prefer to sell companies rather than out-license their products, and we believe the most attractive companies for acquisition are those developing products in chronic inflammation, oncology, cardiovascular disorders and infectious diseases.

Moreover, our analysis showed that acquisitions by large pharmaceutical companies were generally in line with their official declared partnering interests, and when this was not the case, the deal value was lower than the average. This suggests that biotech entrepreneurs should not spend much effort in attempting to approach big pharma buyers with assets that are outside their indicated partnering interests. If they do, they will find lower valuations on the table.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available at http://www.nature.com/doifinder/10.1038/nbt.2533.

1. Big Pharma Mega-Mergers 1995–2014, http://www.datamonitor.com/kc/pharma/
2. Nutt, D. & Goodwin, G. *Eur. Neuropsychopharmacol.* **21**, 495–499 (2011).
3. Tufts Center for the Study of Drug Development. Impact report: new or modified indications for existing drugs have steadily increased in U.S. **13**(2) (Tufts University, March/April 2011).
4. Silicon Valley Bank. Continued rebound: trends in life science M&A. <http://www.svb.com/uploadedFiles/Blogs/10079/continued_rebound.pdf> (July 2012).
5. Daghlian, M. Life sciences M&A sees fewer billion dollar deals. *The Burrill Report* (4 January 2013).

SciCafé nature publishing group npg

Startups on the menu

Boston University's (BU) Jim Collins presented work from his lab on a network biology approach to antibiotic discovery at the Boston SciCafé, *Nature Biotechnology*'s and *Nature Medicine*'s tri-annual gathering of academic researchers and business people. He's now a cofounder of EnBiotix, a startup focused around this technology, to develop new classes of antibiotics and antibiotic potentiators to tackle multidrug-resistant microbes. *Nature Biotechnology* talked to him about the company.

Nature Biotechnology: Describe the process for how EnBiotix came together.

Jim Collins: Jeff Wager and I met in the fall of 2011, via BU's Office of Technology Development. Jeff was looking for new commercialization opportunities in biotech, and I was looking to partner with a serial entrepreneur to commercialize our antibiotics platforms. We met extensively over several months, and by the time we headed into 2012, we had already decided to form EnBiotix. Jeff reached out to NAEJA Pharmaceutical and Great Lakes Drug Development and brought them on as cofounders, in addition to Apeiron Partners and BU, and officially named the company and issued shares to co-founders in July 2012.

NBT: What programs are you prioritizing within the company?

JC: Our top priority within the company is our reactive oxygen species (ROS) program—we are working to find small molecules that enhance the endogenous microbial production of ROS and can be used to potentiate the bactericidal activity of existing antibiotics against Gram-negative bacteria.

NBT: What do you most enjoy about starting a company?

JC: I am most intrigued and excited by the challenges of transforming a project into a product.