

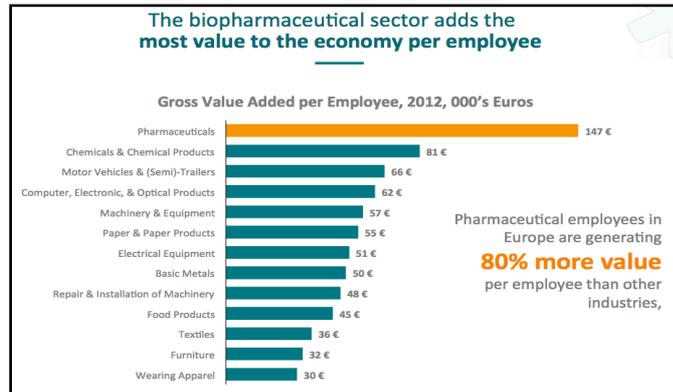


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# Europe's flawed and underfunded Biotech-ecosystem

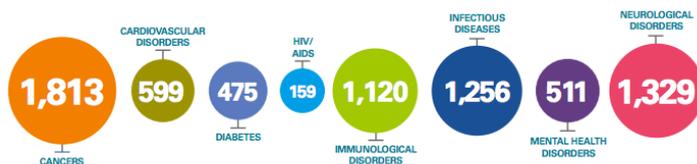
## - EBE position paper -

Biotechnology<sup>a</sup> is important for Europe: the sector helps the economy grow and provides new jobs, while supporting public health. In 2015, more than 10.000 new jobs were created in the biotech industry in Europe and 93 medicines for human use were recommended for market authorisation by the European Medical Agency with 39 new active substances, most of which are biopharmaceutical products. Europe has world-class research institutions, and a host of novel innovative drugs that are making their way through the clinical development phase. Being at the competitive edge of innovation in the



Note: Europe is defined here as the EU-28 plus Norway; Gross value added for each industry is defined as the gross income from operating activities per employee. Source: Health Advances analysis; Eurostat Database (accessed February 2016).

WITH OVER 7000 MEDICINES IN DEVELOPMENT, THE EXCITING NEW WAVE OF MEDICAL INNOVATION WILL PLAY A KEY ROLE IN ADDRESSING THE CHALLENGES FACED BY PATIENTS AND HEALTHCARE SYSTEMS



biopharmaceutical field is crucial for continuing to deliver on novel medications, new jobs and economic growth<sup>1, 2</sup>. If Europe wants to remain at this competitive edge, a number of strong and novel actions must be implemented across the European Union and its Member States.

### Summary

Europe, despite year-on-year growth, is increasingly lagging behind the US in creating a mature biotech funding ecosystem. This results in significant capital leakage and innovation drain to regions outside of the continent. In this respect, Universities and research institutions need to play a much more important role by increasing the entrepreneurship of scientists and Technical Transfer Offices (TTOs), with the aim to improve Europe's translation capability of basic science into commercial ventures. On top of that, we need to implement measurements to create a strong specialist investor community and an optimally functioning single capital market in Europe for biotech companies, in order to prevent that other regions than Europe will economically benefit from the excellent basic science that Europe generates.

### European Science & Technology Transfer

Europe's basic science is competitive with any region in the world and there is no structural difference in quality of science compared to specific regions in North America or Asia<sup>3, 4, 5</sup>. However,

<sup>a</sup> Biotechnology is the use of living systems and organisms to develop or make products, or "any technological application that uses biological systems, living organisms or derivatives thereof, to make or modify products or processes for specific use" (UN Convention on Biological Diversity, Art. 2). In this text, the term 'biotechnology' and 'biopharmaceuticals' companies are used interchangeably and refer to companies or products meeting the definition in the first sentence, whereas pharmaceutical companies make mostly small molecule medicines with a chemical basis. Whilst most classical pharmaceutical companies nowadays are adding biotech products to their portfolio, companies like Amgen or Gilead grew on the strength of their biotech products and are considered typical biotech companies.

a fundamental issue in Europe is its translation capability of basic science into a commercial venture, in particular on the aspects of defining an attractive business case and finding sufficient investment capital to execute a viable business plan.

Strikingly, some of the most interesting discoveries that are currently applied to products in development originate from European institutions but are predominantly employed by US companies: RNAi<sup>b</sup>, CRISPR-Cas9<sup>c</sup> and next-generation T cell receptors. This means that other regions than Europe are reaping the economic benefits from Europe's excellent basic science.

**CRISPR/Cas9**, a promising gene editing technology, has been co-discovered in Europe, but sees its further development predominantly pursued in the US. Recently, the three major companies in this field, all headquartered in Cambridge (MA), raised some large amounts of capital: **Editas Medicine** (\$120 million), **Intellia Cambridge Therapeutics** (\$70 million) and **CRISPR Therapeutics** (\$64 million). The newly raised capital shall be used for hiring new employees and doing investments in the region. Interestingly, CRISPR Therapeutics started its operations in Basel, Switzerland, but partially moved its headquarters to the US as part of its latest financing round.

Europe may be more risk adverse and there is no "license to fail" for entrepreneurs, but foremost there is no strong culture of institutions or individuals seeking useful application of their work, taking out patents and creating start-up companies<sup>6</sup>. At European universities, science students are not offered courses in entrepreneurship; a better integration with business schools would be beneficial for creating a culture of entrepreneurship amongst scientists. For example, US universities train and incentivize scientists, and it is not uncommon to have serial biotech entrepreneurs based at the universities<sup>7</sup>. Training of scientists in business and management aspects would in the long run also address the need in Europe of well-trained and experienced management within biotech companies. Currently, scientists with business and management experience are mostly found close to pharmaceutical companies in Denmark, Switzerland and Belgium, where in consequence many biotech companies are found as well. In general, however, European biotech companies do not seem to have the ability to attract experienced senior managers that have worked in multiple small biotech companies and have a successful track record<sup>8</sup>.

Another problem at European universities is the lack of realism and experience at TTOs, negotiating unrealistic equity shares in spin-off companies and distributing revenues predominantly to the universities themselves. In most cases, this leads to lengthy negotiation processes, frustrated scientist-inventors and loss of momentum in terms of business opportunities. One apparent reason for such underperformance is that most TTOs at European universities are poorly financed and do not have the ability to attract and train experienced staff. A survey in a Nature publication<sup>9</sup> has shown equity shares of universities ranging from 1% to 50% with US universities having the lowest, most realistic rates.

Recommendations:

- Business and Management training should be provided to scientists across European universities and research institutions
- Adequate funding of TTOs and more entrepreneurial awareness at European universities should be created: only when innovative ideas are actually put into practice will they result in economic growth, new jobs and welfare for society.

<sup>b</sup> **RNAi**: RNA interference (RNAi) is a biological process in which [RNA](#) molecules [inhibit gene expression](#), typically by causing the destruction of specific [mRNA](#) molecules. The pathway is investigated to develop therapies for viral infections, neurodegenerative diseases and cancer.

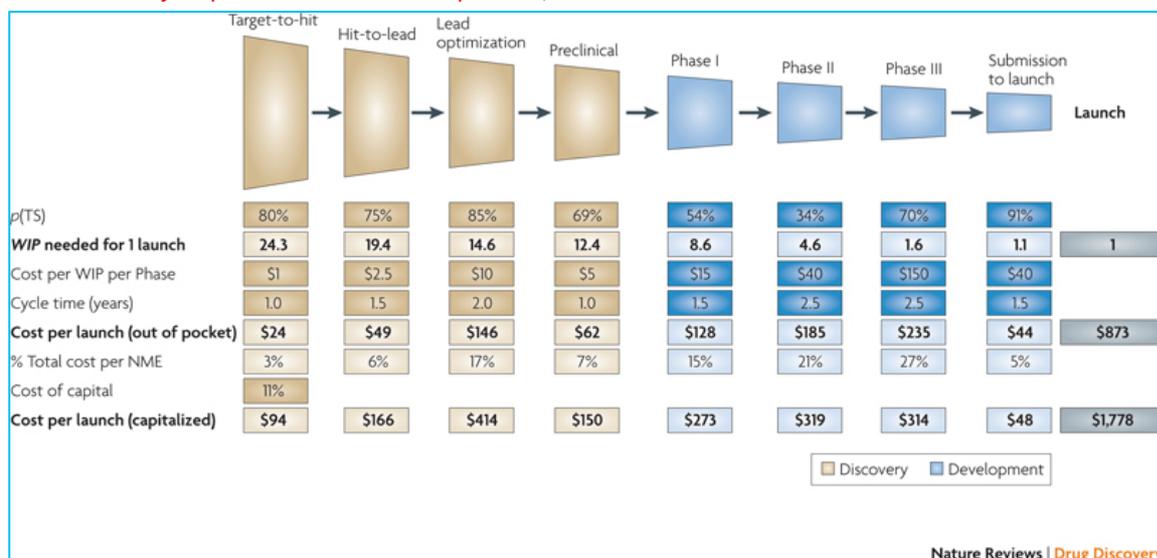
<sup>c</sup> **CRISPR-Cas9**: Clustered regularly interspaced short palindromic repeats (CRISPR) are segments of prokaryotic DNA containing short repetitions of base sequences. Each repetition is followed by short segments of "spacer DNA" from previous exposures to a bacteriophage virus or plasmid. The CRISPR/Cas system is a prokaryotic immune system that confers resistance to foreign genetic elements such as those present within plasmids and phages, and provides a form of acquired immunity. The Cas protein(s) use the CRISPR spacers to recognize and cut these exogenous genetic elements in a manner analogous to RNA interference in eukaryotic organisms. By delivering the Cas9 nuclease and appropriate guide RNAs into a cell, the cell's genome can be cut at a desired location, allowing existing genes to be removed and/or new ones added. Cas9 was the first nuclease discovered. Other such systems are thought to exist.

## European Funding Ecosystem

There is significant public research funding available in Europe such as the public-private partnership Innovative Medicines Initiative (IMI), the European Commission’s Horizon 2020 and InnovFin, the joint initiative launched by the European Investment Bank Group (European Investment Bank (EIB), and European Investment Fund (EIF)) in cooperation with the European Commission under Horizon 2020. These are perceived as good funding vehicles for biotech companies. In order to be even more attractive and efficient, these research funds need to be careful not to divide the funding too thinly over all candidates, and across different countries. Instead, the focus should lie on the quality of the research with the aim to fully exploit its scientific and commercial potential.

The number of European seed<sup>d</sup> and series A rounds<sup>e</sup> have increased over the past five years and European investors currently collect more money in their funds than ever before. However, taking into account the investments needed to develop biopharmaceutical products for market launch, the total amount of European Venture Capital (VC) money is by far too low to finance European biotech companies throughout the whole product development process. Mature biotech companies, meaning companies that are able to develop, launch and sell a medicinal product independently, are lacking in Europe. Such mature biotech companies are essential for a confident biotech investment ecosystem, as they generate revenues and are driving the interest of investors. In 2015, the top five commercial biotech companies in the US accounted for revenues of 80 billion USD, representing half of the worldwide revenues in biotech. It is evident that such revenues from mature biotech companies create a healthy investment ecosystem that attracts novel investments. With respect to the maturation of biotech companies in Europe, only 13% of its Phase II companies manage to move into Phase III or beyond, leading to a significant loss of innovation. Most other companies do not find their funding in Europe, but instead move to the US seeking a listing on the NASDAQ<sup>f</sup> or acquisition by a larger, often US based company, representing a huge innovation drain from Europe to the US.

**Table 2: Cost of biopharmaceutical development**<sup>g, 10</sup>



<sup>d</sup> **Seed money**, sometimes known as **seed funding** or **seed capital**, is a form of [securities offering](#) in which an investor invests capital in exchange for an equity stake in the company. The term *seed* suggests that this is a very early investment, meant to support the business until it can generate cash of its own (see [cash flow](#)), or until it is ready for further investments.

<sup>e</sup> **Series A rounds** are traditionally a critical stage in the funding of new companies. Series A Preferred Stock is the first round of stock offered during the seed or early stage round by a portfolio company to the venture capital investor. Series A preferred stock is often convertible into common stock in certain cases such as an IPO or the sale of the company. The capital raised during a Series A is usually intended to finance the company for 6 months to 2 years as it develops its products, performs initial marketing and branding, hires its initial employees, and otherwise undertakes early stage business operations.

<sup>f</sup> **NASDAQ**: **N**ational **A**ssoiation of **S**ecurities **D**ealers **A**utomated **Q**uotations, the key US stock exchange for biotech companies.

<sup>g</sup> Acronyms used in Table 2: WIP = work in process, i.e. number of assets; NME = new molecular entity

In 2015 European companies have raised more capital than ever, but it still represents only a fraction of the capital raised by US companies. Europe is losing even more of a competitive edge, when comparing the modest increase of 6% in capital raised over 2014 to the 35% increase in capital raised by US companies over the same period. The huge increase in the US is fuelled by the presence of mature biotech companies launching medicinal products independently, and generating significant revenues for biotech companies that otherwise would have gone to their pharma partners. These large revenues are drawing the interest of more investors to the biotech space.

*Capital raised, number of companies & employees in US vs EU (2014 vs 2015)\**

	US (2014)	US (2015)	EU (2014)	EU (2015)
<b>Capital raised by companies</b>	\$45,1B	\$61,1B (+35%)	\$9.3B	\$9.9B (+6%)
<b>Number of companies</b>	2.763	2.772 (+0%)	2.268	2.259 (0%)
<b>Number of employees</b>	109.450	131.690 (+20%)	61.320	72.160 (+18%)

\*Source:Biotechnology Report 2016 EY

Apart from a few companies such as Shire Plc (Ireland), UCB (Belgium) and Actelion (Switzerland), Europe lacks mature biopharmaceutical companies that generate significant revenues from the sales of their innovative products.

Considering the amount of capital raised by European biotech companies, the number of companies and the amount of money necessary to put a medicinal product on the market, it is evident that the European biotech ecosystem is heavily underfunded. Little maturation of biotech companies can be expected in Europe in the near future. Even large European funds find US companies more compelling cases for investment than Europe-based companies, basically because US companies create a much higher value and greater return on investment. Some of these funds even invest 80% of their money in the US, with only 20% in Europe<sup>11</sup>: a big leakage of capital for innovation from Europe to the US.

In addition, venture capital firms in Europe are perceived as too small in fund size and sometimes are geographically limited in their investments. The EIB and EIF are important bodies within the European Union to provide long-term financing, including the funding of venture capital firms, but as with the IMI, funding is spread too thinly over the different venture capital firms. Both EIB and EIF, when financing investment funds, should provide funding with the aim of creating larger funds that can invest across Europe. Furthermore, it is crucial for a healthy biotech investment ecosystem to create crossover investors that can invest in a biotech company both when it is private as well as in its public phase, in addition to the classical VC funds that invest in private companies. Whenever crossover investors are involved in a biotech company, their way to the stock market is made easier and the performance after an Initial Public Offering (IPO) as well as the liquidity of the stock is much better. The perspective of a good after-IPO performance is important for attracting the interest of investors in private biotech companies, as this is perceived as a possible exit for the investors. There are many crossover investors in the US, mostly with deep pockets. In the EU there are only a few small crossover investors, while there is clear need for at least two of these large investor funds that could help developing the capital markets and providing exit opportunities for investors in private biotech companies.

Recommendations:

- EIB/EIF to make large financial tickets available for creating at least two large independent European Biotech crossover investors with budgets of more than one billion Euros;
- EIB/EIF, when financing investment funds, to provide funding to larger European Biotech venture capital funds that can invest across Europe;

- European research funding for biotech to focus on quality and sufficient funding to address the scientific potential.

### Capital Markets and other incentives

Europe needs to build a bigger and better capital market for biotech companies to overcome the funding gap that prevents the needed growth of the biotech sector. Capital markets in Europe are fragmented national markets with separate rules, regulations and business practices and provide little liquidity for investors in biotech companies. Furthermore, capital markets in Europe are not deep enough to take up any downturns, necessary to create trust and continuity in a highly risky sector such as the biotech industry. Without such a deeper capital market, Europe will not be able to create a mature biotechnology sector able to generate sales from the products developed in-house. We appreciate the activities undertaken by the European Commission to build a true single market for capital – a Capital Markets Union for all Member States –, but we believe that specific measures for the biotech sector should be taken.

Because of the suboptimal functioning of capital markets for the biotech sector in Europe, an IPO for a biotech company is not generally seen as an exit option for venture capital investors. They rather see their European portfolio companies being acquired by another company, in most cases a larger US based company, than taking them to the European stock market. Low liquidity and negative post-IPO performance are being perceived as drivers for such preferred behaviour. In the US, there is competition between acquisition and IPO as exit strategies, resulting in a much higher value in both situations and thus greater return on investment for the investors.

**ArGEN-X (Ghent, BE), Affimed (Heidelberg, DE) and Five Prime (San Francisco, US)** are antibody companies in the field of oncology, all with a similar clinical stage of development. ArGEN-X is listed on the Euronext with a market cap of €176M, while Affimed and Five Prime are both listed on the NASDAQ; the German based Affimed with a market cap of \$96M and the US based Five Prime with a market cap of nearly \$1.4B. These companies were listed within a year time frame between Sept 2013 – Sept 2014. Compared to their introduction price, their stock price performed markedly different: ArGEN-X +31%, Five Prime +288% and Affimed -58% (dd 3/8/2016).

There is a strong trend of European biotech companies being listed on the NASDAQ. In general, these companies raise almost double the amount than that raised by companies listed on Euronext and AIM, however, Euronext companies show much stronger after-IPO performance compared to an overall negative post-IPO performance of European firms listed on NASDAQ. This creates a momentum for a united European capital market for biotech IPOs, accelerating the European venture capital industry to become the same size relative to the economy as in the US and provide funding for future potential European

‘Amgens’ and ‘Gileads’ that are now not getting the funding in Europe.

Additional concessions to stimulate greater investment, currently randomly (haphazardly) available at national, or sub-national level, such as tax credits for research or specific commercialisation agreements for Intellectual Property (IP) developed at European universities through investors in biotech start-up companies can present strong incentives to biotech companies and assist in obtaining longer term funding. Rolling out the most successful of such incentives in a manner that creates synergies across Europe, for example in form of EU Commission supported and Member States implemented Best Practices to incentivise innovation, would provide additional support to establishing successful businesses in Europe based on innovative ideas developed in Europe.

Recommendations:

- European Commission to facilitate a single capital market for biotechnology companies;
- European Commission and Member States to facilitate European tax incentives and other incentives for investing in private and public Biotech companies through identification of Best Practices

## Conclusion

Europe has great science in the biotech sector but lags behind in translating the science into successful businesses. Addressing the key factors contributing to a migration of business ventures outside of Europe identified by the European Biopharmaceutical Enterprises (EBE) would improve the current gap in translating innovation into businesses. The recommended key actions focus on improving technology transfer and business acumen of innovators, specific actions within the European funding ecosystem to improve investment within Europe, speeding up development of a single capital market for biotech companies, supplemented by identification and Europe-wide implementation of best supportive incentives across Europe such as tax credits for research and IP commercialization agreements with investors in biotech companies would provide further incentives to establishing biotech companies in Europe.

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