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THE EUROPEAN LANDSCAPE OF LISTED BIOTECH COMPANIES

2018 REVIEW

The European landscape of listed biotech companies: 2018 review

This review is an introduction to the universe covered by Biotellytics, publisher of biotechradar.eu, a business intelligence service on the landscape of the European biotech companies listed on the main European stock exchanges. This service aims at providing insights and data at company level for investors, as well as consolidated data for the European level for life sciences professionals. This review will form a basis for more content to be released in the future.

This document is intended for a broad audience but more particularly people who are already specialized in the life sciences, without being familiar with the European biotech landscape, and notably the listed side.

After a definition of our universe, and a presentation of our selection, we will provide a global overview of the landscape for 2018, based on the following items: IPOs, M&As, R&D pipeline, commercial products, market data, employment, financing and other financial metrics, and deals. All these data will be broken down by country or by (country) cluster, when relevant, in order to have a minimum number of companies for each presented data. Belgium (BE) and the Netherlands (NL) will be taken together, as well as UK and Ireland (IE). Norway (NO) and Finland (FI) will also be gathered into a cluster. The same way, Italia (IT) and Spain (ES) will form the “Southern Europe” cluster. We will end by a snapshot of the characteristics of a “typical” European public biotech company, at the end of 2018.

Introduction

The European biotechnology (“biotech”) sector is an ecosystem in the making. The first listings of biotech companies (our universe) were only recorded in the late 90s, so roughly 20 years ago. The inception of biotech companies, listed later on, started accelerating around this period, so 10 to 20 years later than the emblematic Amgen, Biogen, Celgene and Gilead Sciences. The biotech sector is not yet established as a strong pillar in the European markets, even though one can exceptionally find some biotech companies selected in the main national indices, e.g. in Belgium. It’s very recent though.

In contrast, the Healthcare sector and particularly the Pharma segment is well represented in Europe, with 4 European Pharma companies in the Top 10, and 8 in the Top 20, according to GlobalData [1] (we do NOT consider Allergan as an Irish company). Another testimony of the relative strength of the European Pharma sector is the weight of the sector in the total equity market cap, measured to 7.6% (1.05 trillion USD at the end of 2018 for 28 companies -broad “Pharma” definition-, out of 13.2 trillion USD of total market cap among the 8 main European stock market operators [2-4]). This is higher than the US figures, with 1.5 trillion USD for 12 US Pharma companies [1;5], out of 30.4 trillion USD of market cap, or 4.9% [6]. Unfortunately, the European Biotech segment only weights 0.37% of the total European market cap, or 50.3 billion USD (155 companies in our universe), whereas the US Biotech segment represented 1.1% of the total US market cap, or 336 billion USD for 444 US companies listed on the Nasdaq in New York (diagnostics and services excluded).

This lag in Europe owes mainly to the overall lack of financing available for the Biotech segment, with few exceptions nonetheless. Some reasons can be found in this review. For the solutions, there are unfortunately no easy ones. In a recent thought-provoking article named “Is Going Public in Europe the Kiss of Death?” [7], Antoine Papiernik, Managing Partner at Sofinnova Partners (an important Life Sciences fund in Europe), invited the European companies aiming at an IPO someday to “think as if they were located in Boston”, and to engage as soon as possible with the investors with “deep pockets”, namely those in the US and why not those in the fast-growing Hong-Kong markets. In his guidance, Europe would a second choice, but paradoxically 3 out of the 4 companies mentioned as having “cracked the code” (multi-billion USD market cap) were actually listed on European markets first. Moreover, a direct listing in the US is probably not for the mainstream private biotech company, e.g. for market cap considerations. This is indirectly implied in the article, as it relates to companies with “science, products, management, and investors on a par with the best Boston-based companies”. So yes, the European ecosystem needs success stories à la Actelion, and companies who remain independent -Galapagos!- to show the way, even if this is the natural order that most of them are acquired. A few are on their ways and need to end the job from a commercial standpoint. With the pipeline data we show in this review, there will likely be more.

At the same time, more positive signals are sent from the private side. Over the past couple of years, we started to see inflated early VC rounds on European biotech companies (e.g. 40 million EUR in series B for Enyo Pharma in June 2018 [8], or 67 million EUR in series A for Alizé Pharma in July 2019 [9], just to name a few), mimicking a trend recently observed in the US [10-11]. Therefore, it will be interesting to follow in the coming years what will be the VCs’ exit model when these companies reach a stage of development legitimating an IPO. One could guess a direct listing on Nasdaq.

Unfortunately, we do not have any particular insights to provide on why the health in the private and public sectors would be so divergent, especially in the long term.

The overall ecosystem needs to gain in maturity at all stages: executives, governance, analysts, VCs, investors of all kind, media, etc... (and service providers like biotechradar.eu!). Maybe just incantations today, because this is a process. There is still a long way for the European retail investors to get “educated”, but it is probably only a matter of time as well. The risk-averse profile of the typical European investors at baseline, at least as compared to the US, is also a hurdle. Perhaps we in Europe also do not showcase our success stories enough, as compared to the US, at least from one country to another. There are signs that we try to learn the lessons from the recent successes, and hopefully from setbacks as well. The regulatory environment can certainly be improved in some countries, to support the clinical research. Finally, the European politics probably do not see any reason to help the biotech ecosystem in particular, as the Pharma sector is still relatively healthy. Perhaps the European biotech sector needs more visibility and more lobbying, in general and as an innovative industry segment.

Innovation drives growth, this is a constant everywhere in the world, and in every business. Over the past decade, the biotech sector has become a main vector of innovation in the drug industry, not only to fuel the pipeline of the largest Pharma companies, but also to bring treatments on the markets on their own [12-13]. At some point, a strategic question in Europe could be: who do we want to buy our drugs from? There is no news here, but Europe lacks tech leaders. If we cannot build digital giants, why not relying on what is still recognized as a strength: the quality of the science and scientists? At least those who do not leave Europe for better opportunities overseas.

Unfortunately, there is no equivalent to the Nasdaq markets in Europe. Beyond investment policies excluding investment on European assets like biotech companies, some international investors might just view the European markets as not worth the effort. If we take the US investors for example, they only have to deal with one market place (Nasdaq), one regulator (the SEC), all the documents are in English, and the market offer is large (more than 500 companies for pharma/biotech only). This is simple. Now, if you look at the main European countries and stock markets, like our universe, you need to deal with 13 countries, with the same number of Financial Supervisory Authorities and stock exchanges, managed by 8 stock market operators. The main corporate documents can mostly be found in English, but not always, so you basically need to deal with 10 languages. On top of that, not all the countries in the European Union have adopted the euro, so you also need to deal with 7 currencies. And this for 150-200 companies (biotech/pharma only), with select companies already accessible on the US markets with the dual listings (excluding those who directly list in the US). Several of these items might be minor hurdles for professional investors, wherever they are based. Perhaps there is even no hurdle at all for some. But it seems fair to say that this is less simple than in the US. This is basically one of the purposes of the service offered on biotechradar.eu, presenting the whole European landscape as one, while keeping the granularity at company level. In short, making things easier for investors. The US investors’ referential also needs a reset, or at least an adaptation when they look at Europe, e.g. there is no such thing as same-day offerings after “positive news”.

Additionally, Europe lacks a cluster as strong as Boston, but given the fragmented nature of this territory, it is not likely to happen anytime soon, as each country also aims at becoming a future leader. Instead, there are several regional “bio-clusters” in each country. The fragmentation we just

highlighted may also be reflected in the profile of some companies, with a lack of critical size. Would the ecosystem benefit of a local consolidation, e.g. of businesses relating to very close therapeutic areas or modalities?

Another point is the rise of a new hotspot for Life Sciences in Hong-Kong, which now both competes with Europe to attract US capitals, but could represent an opportunity as well in the future, according to Papiernik's take. In reality, there might be just no competition properly speaking, if we refer to the large amounts of money flowing in Hong Kong, as compared to Europe. However, this is still a "work in progress" in Hong-Kong as well [14]. Indeed, the biotech stock performances were very mixed in Hong Kong in 2018 [15], and one will have to judge over a longer period. What is certain is that in terms of Business Development, Asia must be considered. So, Hong-Kong, Asia, China, threats or opportunities for Europe, only time will tell.

After all these points, the "elephant in the room" question is: why on earth would anyone invest in European listed biotech companies? Ask the likes of Fidelity, Perceptive Advisors, Baker Bros, just to name a few, they will probably have a clue. These specialized funds definitely do not wait for a company to list on Nasdaq in New York to take a bite. There are opportunities everywhere, and the sector rewards the best cases. Therefore, when all the boxes are ticked, Europe or not Europe, does it really matter? Of course, there might be no plethora of opportunities on the old continent, but they exist. This is even a pity that the European investment firms do not capture a larger share of the upside from the most promising European biotech companies. On the other side, there are already several hedge funds operating on the European biotech sector. Looking at the pipeline data in this review, the aficionados of the event-driven strategy will not lack opportunities either. Finally, even if selectivity is key in biotech investing, requiring key data at company level, it is also interesting to know the sector characteristics, at top level, which is the purpose of this review.

Is there a future for the biotech sector in Europe? Will the public sector recover from a tough period? How long will it take? How will the financing environment evolve moving forward? Is a consolidation of the number of companies needed? What are the main characteristics of the listed segment of the European biotech sector? Are there different dynamics among the European countries? Who will be the next European rising stars? Will the soon-to-be integrated companies succeed in their transformation process? These are just few themes and questions we will try to cover, or that we will help the investors and life sciences professionals to find the answers to, not especially in this review but in general, so stay tuned.

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1. The European landscape of listed biotech companies: definitions, selection, general overview

Like in a clinical trial, our selection globally meets some inclusion and exclusion criteria, with few exceptions. We tried to build a list of companies to have a relatively homogeneous group, or the least heterogenous to be more accurate, and limit the number of outliers. These criteria can be found below. We reviewed the activity of all the companies, and checked the consistency of their business model with the above-listed criteria.

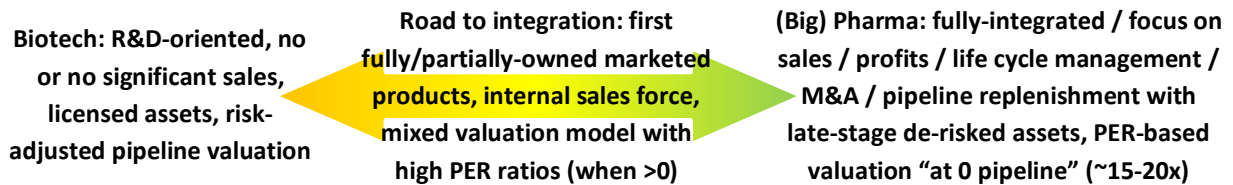
Inclusion criteria:

- Inception in one of the main European countries: France, Germany, UK, Italy, Spain, Belgium, Netherlands, Switzerland, Denmark, Sweden, Norway, Finland, Ireland
- Primary listing on (at least) one of the main European stock exchanges, including the following:
 - Euronext, Main market & Euronext Growth: Paris (France), Brussels (Belgium), Amsterdam (Netherlands)
 - Deutsche Börse XETRA: Frankfurt (Germany)
 - SIX Swiss Exchange: Zurich (Switzerland)
 - London Stock Exchange & its Alternative Investment Market/AIM: London (UK)
 - Nasdaq OMX - Nordic List & First North: Stockholm (Sweden)
 - Oslo Børs: Oslo (Norway)
 - Bolsa de Madrid: Madrid (Spain)
 - Borsa Italiana: Milan (Italy)
- Companies developing therapeutics, with a focus on the development of their innovative pipeline, including some “specialty” companies, and some companies developing generics/biosimilars (broad “biotech” definition engulfing both “biotech” and “pharmaceuticals” as per their original definitions, called “biotech” for simplicity's sake)
- Companies whose market capitalization/enterprise value essentially relies on their pipeline, or in a mix of their pipeline and their product sales/royalties and not only on sales/profits
- “Large” biotech companies without a fully-owned product at the commercial stage, not yet vertically-integrated

Exclusion criteria:

- European companies directly listed outside Europe (basically on Nasdaq, New York, US), without any secondary listing on the main European markets
- Foreign companies (for which Europe is not considered as their “domestic” territory)
- Pharma companies or pharma-like vertically-integrated companies (valuation with a PER, focus on sales/external growth, or limited innovation in the pipeline)
- Medtech/Diagnostics companies (non-core activity for some companies in our selection)
- Service companies: CROs, CMOs, Drug Discovery companies (very few exceptions for this particular activity), API providers, etc...
- Biotech Funds

All the companies included in our selection (see **Table 1**) are at various stages of development for their drug candidate(s). While some companies might remain on the “biotech” side forever, others might become partially or fully-integrated “pharma” companies (depending on manufacturing integration). On the other way, integrated companies might be forced to become “biotech” again if their pipeline was not filled adequately. Therefore, both the position and the direction within the “biotech-to-pharma” transition process (represented just below) mattered for our selection.



However, our selection includes some outliers or special cases, either not meeting the aforementioned criteria, or subject to discussion. The most relevant cases can be found below (list not comprehensive):

- Evotec (Germany): a company offering integrated drug discovery services, leader on IPSC-based drug discovery. It is selected because of its high-growth/innovation profile;
- Oncodesign (France): another drug discovery company, much smaller than Evotec and with a slightly narrower scope of services compared Evotec but also converging towards an integrated drug discovery model, leveraging its kinase inhibitor platform at the same time. It is basically selected for historical reason;
- Nanobiotix (France): some might consider this company as a medtech (their lead product was regulated as a medical device for their first marketing authorization in Europe), however their model is the one of a biotech, and their product is aimed for a therapeutic use (the regulatory pathway in the US remains to be defined);
- Cosmo (Italy): a specialty pharma focused on GI diseases with therapeutics & medical devices on the market, still with many drivers in the pipeline. The US patent of their lead UC drug will fall next year. We thought it was relevant to have it included in the pool;
- Vectura (UK): a company specialized in COPD/asthma treatment, developing both formulations (CS/LAMA/LABA) and medical devices (inhalers) with partners, included in our selection but under watch as the business model is shifting towards a “specialty CDMO”;
- Indivior (UK): a leading company specialized in addiction and more specifically of opioid addiction, de-merged from Reckitt Benckiser Pharmaceuticals in 2014. It can also be considered as a specialty pharma but contrary to Cosmo, the patent cliff for their leading drug is happening right now, which forced the company to reshape its long-term strategy and portfolio. We thought it was legitimate to have it into our selection;
- Oxford Biomedica (UK): a company with mixed model consisting in manufacturing services & supplying viral vectors for cell and gene therapies, along with developing both an internal pipeline and supporting a partnered pipeline (mainly gene therapies with 1 CAR-T program). Given that the valuation is not (yet) massively dominated by the service segment, we feel that the company is still a relevant pick in our selection;
- Allergy Therapeutics (UK): the company name speaks for itself. The company already has several products on the market (some only on a Named-patient basis) but still has a decent R&D pipeline to be included in our review;

- Basilea (Switzerland): spin-off from Roche in 2000, it is also a commercial stage company that was originally focused in infectious diseases. And like many players in this field, the company has broadened its scope with the addition of oncology assets, with some innovation pending in the pipeline and therefore justifying the presence in our selection;
- PharmaMar (Spain): a conglomerate that is definitely turning into a pharma-only business model, particularly in oncology, with the divestment of 2 group subsidiaries (consumer chemicals in 2018 and cleaning, cleansing, disinfecting products for the industry very recently in 2019). The company has 2 oncology drugs on the market but only 1 available in the US and Europe. We also judged it was a fit in our selection.

In addition, some companies are covered on our service, but are not included in this review, either because their profile is too singular, or because their business model is transitioning outside the core “innovative biotech” segment we cover here. This includes the following companies:

- Circassia (UK): a company specialized in respiratory disease who acquired the rights of several assets, but also proceeded to a complete write-off of its innovation pipeline in asthma/COPD and allergy over the past couple of years, following multiple clinical trial failures. Therefore, the business model, coupled with a fully depleted innovation pipeline, makes the company out of the scope of this review;
- Biotest (Germany): the company specialized in plasma-derived products/IVIg is in complete transformation at several stages, after a strategic refocus initiated in 2015 and a change of control of the company taking place 2 years ago. It's now in the hands of Creat Group from China via its German subsidiary Tiancheng, but it was not de-listed because of a 2-level share scheme (Voting rights majority via Preferential Shares). This takeover led them to divest their US business to comply with antitrust rules. The company is also about to be brought in kind by Creat as part of a capital increase into Shanghai Raas. Biotest is looking to divest their assets outside plasma products (mainly 3 biologics). In anticipation of the completion of all these changes, Biotest is not included in this selection;
- Puretech Health (UK): a very atypical profile, as it is basically a VC fund with an internal pipeline (we cover only this internal pipeline on our service). Given that it is far from being predominant in the group valuation at this stage, we do not include the company in our selection. Also, some would argue that the company mostly operates in the US but still, it was incorporated in the UK, and the company is only listed in London (for now);
- Biotech Pharmacon (Norway): a specialty pharma company whose most of the business relies on its API supplier and animal health businesses. The company has a small commercial product in human health and a cancer vaccine adjuvant in oncology, but considered as non-core, so it is not included in the review (human therapeutic programs covered on our service);
- Sanochemia (Austria): another specialty pharma (not covered), listed on XETRA in Germany, mainly operating as a CMO, but with a partnered product in back pain, once again considered as non-core.

AB Science	FR	Acacia Pharma	UK	A1M Pharma	SE	NOXXON Pharma	DE
ABIVAX	FR	4D Pharma	UK	Active Biotech	SE	Probiodrug	DE
Adocia	FR	Allergy Therapeutics	UK	Alligator Bioscience	SE	4SC	DE
Advicenne	FR	Avacta	UK	Annexin Pharma.	SE	Biofrontera	DE
Biophytis	FR	Destiny Pharma	UK	Asarina Pharma	SE	Cytotools	DE
Cellectis	FR	Diurnal Group	UK	Alzecure Pharma	SE	Evotec	DE
Cerenis Therapeutics	FR	Evgen Pharma	UK	BiolInvent Internat.	SE	Formycon	DE
Crossject	FR	Hemogenyx Pharma.	UK	BioArctic	SE	Heidelberg Pharma	DE
DBV Technologies	FR	Immupharma	UK	Calliditas Therapeutics	SE	Medigene	DE
Erytech Pharma	FR	Indivior	UK	Camurus	SE	Mologen	DE
Genfit	FR	Mereo BioPharma	UK	Cantargia	SE	Morphosys	DE
GenSight Biologics	FR	Midatech Pharma	UK	CombiGene	SE	Paion	DE
Hybrigenics	FR	Motif Bio	UK	Corline Biomedical	SE	co.don	DE
Innate Pharma	FR	N4 Pharma	UK	Cyxone	SE		
Inventiva	FR	Nuformix	UK	Diamyd Medical	SE	GeNeuro	CH
Lysogene	FR	Okyo Pharma	UK	Gabather	SE	Genkyotex	CH
Medincell	FR	Oxford Biomedica	UK	Hansa Biopharma	SE	Addex Therapeutics	CH
Nanobiotix	FR	Realm Therapeutics	UK	Immunicum	SE	Basilea Pharma.	CH
Neovacs	FR	Redx Pharma	UK	InDex Pharma	SE	Idorsia	CH
Nicox	FR	ReNeuron	UK	Infant Bacterial Ther.	SE	Molecular Partners	CH
Oncodesign	FR	Sareum	UK	IRLAB Therapeutics	SE	ObsEva	CH
Onxeo	FR	Scancell	UK	Isofol Medical	SE	Polyphor	CH
OSE Immunother.	FR	Shield Therapeutics	UK	Kancera	SE	Santhera	CH
Pharnext	FR	Silence Therapeutics	UK	Karessa Pharma	SE		
Poxel	FR	Summit Therapeutics	UK	Klaria Pharma	SE	Bavarian Nordic	DK
Quantum Genomics	FR	Synaigen	UK	Lidds	SE	Genmab	DK
Sensorion	FR	Tiziana Life Sciences	UK	Medivir	SE	Oncology Venture	DK
Theranexus	FR	ValiRx	UK	NeuroVive	SE	Orphazyme	DK
Transgene	FR	Vectura	UK	Oasmia Pharma.	SE	Zealand Pharma	DK
Valneva	FR	Verona Pharma	UK	Oncopeptides	SE	Nuevolution	DK
				Orexo	SE	Saniona	DK
argenx	BE	Amryt Pharma	IE	PledPharma	SE		
ASIT biotech	BE			Promore Pharma	SE	Cassiopea	IT
Bone Therapeutics	BE	BergenBio	NO	Sprint Bioscience	SE	Cosmo Pharma	IT
Celyad	BE	Nordic Nanovector	NO	Vicore Pharma	SE	Newron Pharma.	IT
Galapagos	BE	PCI Biotech	NO	XBrane Biopharma	SE	Molmed	IT
Mithra Pharm.	BE	Targovax	NO	Xintela	SE		
Oxurion	BE			XSpray Pharma	SE		
		Faron Pharma.	FI				
Kiadis Pharma	NL	FIT Biotech	FI	Oryzon Genomics	ES		
Pharming Group	NL	Herantis Pharma	FI	PharmaMar	ES		

Tab. 1. List of selected European public biotech companies

Finally, this leaves us with the round count of **150 European biotech companies**, from **13 European countries**, and listed on stock markets from **8 operators**.

Of note, we considered Immupharma as a UK biotech company (this is actually a group with several subsidiaries) but it would not be completely wrong to classify it as a French company either.

If you want to check for more companies outside our “biotech” universe, you can have a look at our **European Pharma dashboard here**, while our **European Biotech dashboard** (including select diagnostic companies) can be accessed **there**.

As a reminder, most of the metrics in this review will be consolidated by country, or by cluster (pooled data from 2 countries).

1.1 Companies by country and by stock exchange

As shown on **Figure 1**, Sweden is the largest provider of biotech companies in our universe, before France and the UK at the same level. Germany is only ranked fourth. Switzerland, the home of 2 European Big Pharma, arrives in fifth. Then follow Belgium and Denmark, 2 very strong places despite their ranking. Finally, Italy and Spain, 2 members of the EU5, have a limited number of biotech companies listed on the European markets, more or less at the same level as the Scandinavian countries like Norway and Finland, and a single company from Ireland.

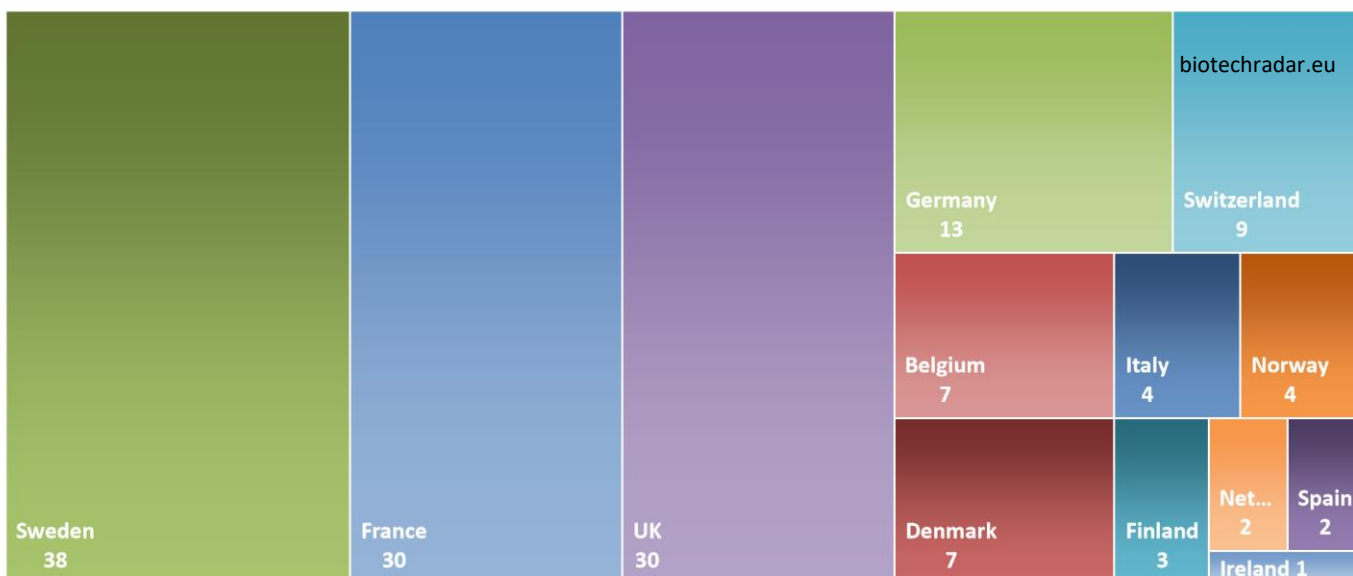


Fig. 1. Repartition of the European listed biotech companies, by country (our universe)

Such a gap between Sweden (10m inhabitants) and much larger countries (> 60m) might come as a surprise for those who do not follow this space. In fact, Sweden is almost an ecosystem on its own inside Europe. In addition, biotech companies tend to list very early in the markets (with respect to their development stage), much sooner than everywhere else actually. In addition, we only included companies listed on Nasdaq OMX Nordic, but there is another platform on which many companies start listing as public companies, before being transferred to the Nasdaq OMX markets later on. This

other platform is the Spotlight platform, formerly known as Aktietorget, allowing companies to list for a small price. Therefore, many Swedish companies floated on Spotlight first, then migrated to the secondary “growth” market of Nasdaq OMX (the First North market). For those reaching even higher valuations, they can finally end on the Nasdaq Nordic List, attracting more investors. Other factors may characterize the Swedish ecosystem: retail investors who are seemingly keener on taking risks than the European average, a well-developed market access, a flow of corporate communications above average, a well-known transparency culture and diligence in reporting. All these elements lead to a favorable environment in this country, at least for the earliest stages. Though, the question of the financing of all these companies will remain for the mid-term, as some of them will move forward into advanced stages, requiring way more funds.

On the other extreme, one might find curious to see so few companies in Italy and Spain. There are many Pharma companies in both countries, public and private, but these countries are not hotspots for the public biotech sector, as of today. However, academia is generally strong in these countries, and some institutions are renowned, so this is not a matter of scientific level. The local ecosystems seem relatively young there, some regional biotech clusters (within the countries) are 10 years old or less. Lastly, most of the Italian companies in our selection played the card of the proximity with specialized investors, by choosing a listing in Switzerland, more than in Italy. This clearly demonstrates a lack of financing support in their home markets. So, is it just a matter of time before the rise of biotech in the south of Europe? Time will tell, but the road will probably be long enough.

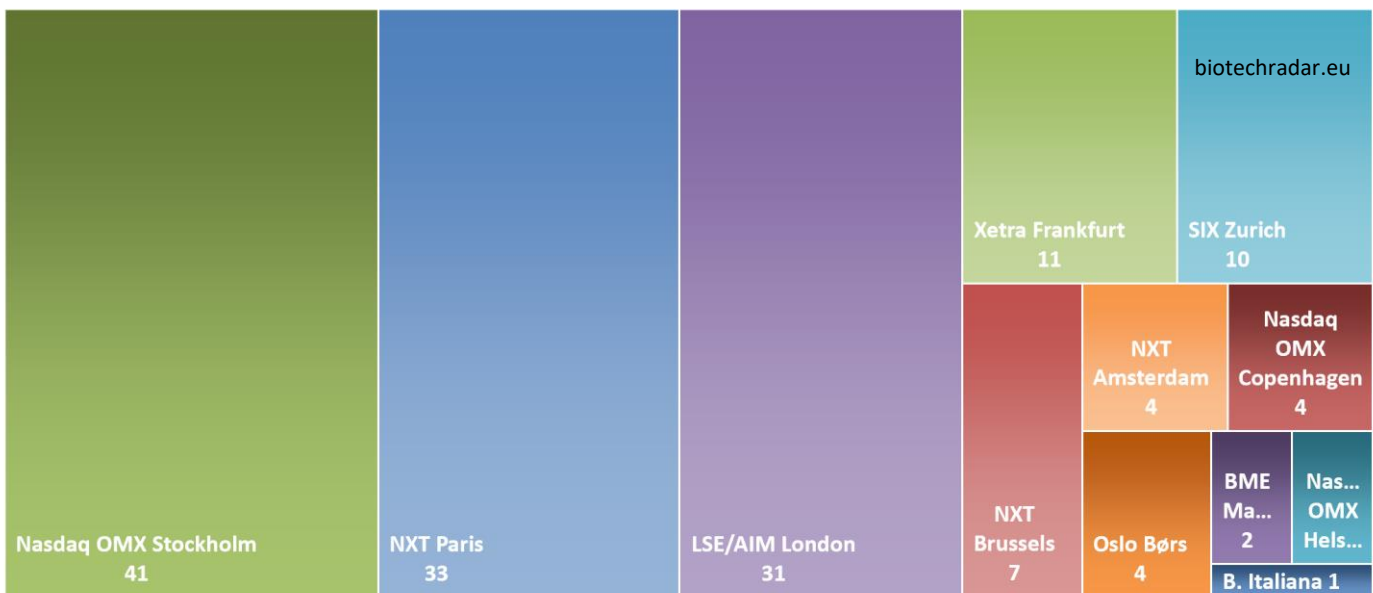


Fig. 2. Repartition of the European public biotech companies, by stock exchange (our universe)

In accordance with **Figure 1**, we find again the 3 main clusters -Sweden, France, UK- when looking at the main stock exchanges (**Figure 2**). As mentioned just before, the country of origin of the companies does not always correlate with the place where it is trading. This is indeed mostly the case (91%), but not always. 3 Italian companies out of 4 are listed in Zurich, 1 German company and 2 Swiss companies are listed in Paris, 1 British company is listed in Brussels, 1 German company is listed the Netherlands, 1 Finnish company is listed in London, 2 Danish companies are listed in Stockholm, and Galapagos (Belgium) is listed in Amsterdam (ok, Belgium and Netherlands are really close!). Finally,

we consider Amryt as an Irish company that is dual-listed in London (AIM) and Dublin (Euronext), but we assigned the main listing as being in London, notably based on trading volume considerations.

The main reasons for these re-locations are, first, a better access to financial resources expected in the targeted listing places, and second, merger and acquisitions, not from the biotech companies but from the stock exchanges. Indeed, Euronext has been very active on M&A in Europe lately: following the acquisition of the Irish Stock Exchange at the end of 2017, the pan-European group just completed the acquisition of Oslo Børs mid-June 2019, after a bidding war with Nasdaq OMX. So, the lead of Euronext will extend again. XETRA (Deutsche Börse) and SIX both host heavyweight biotech companies, but are way behind in total number of companies. Quality over quantity? Or just more pragmatic markets there, less prone to sectorial hype cycles?

1.2 A still relatively young landscape, with an IPO boom over the 2014-2017 period

The dates of inception & IPOs/new listings of the companies in our selection are plotted on Figure 3, sorted from oldest to newest (N.B. these are not the same companies on the x-axis for both series, as data were sorted separately). Also, these IPO/new listing dates only concern the companies in our selection.

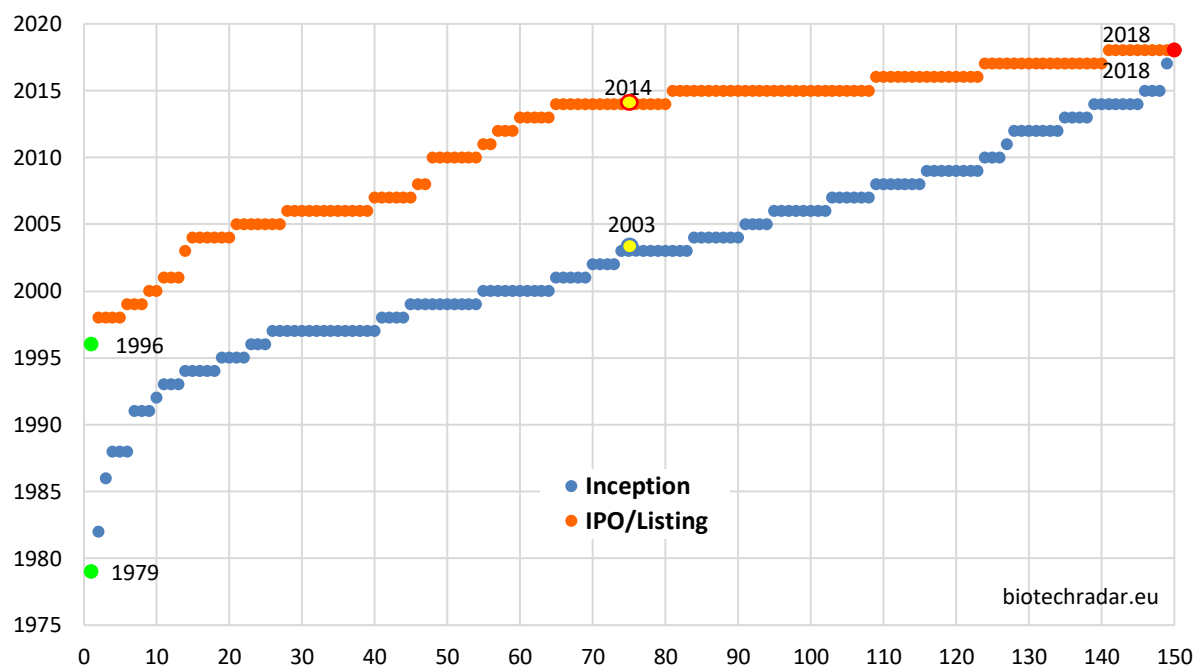


Fig. 3. Inception dates & IPO/new listing dates, sorted (our universe - see N.B. in the text)

At the end of 2018, approximately 27% had 10 years old or less, 50% 15 years old or less, and 72% 20 years old or less since their inception. In short, the age of the companies is quite evenly spread. For spun-off companies, we indicate the year of the spin-off and not the inception year of the parent company. Finally, one could argue that 15 years of median age is not that young. However, the ability to be properly financed in Europe is far from being equivalent to the US, so a straightforward argument is to say that on average, the companies advance more slowly simply because they don't have the financial means to do more and faster.

Moving to IPOs, as shown on **Figure 4**, there was a first peak in 2006 prior to the subprime financial crisis, followed by a real boom during the period from 2014 to 2017. 57% of the companies in our selection started floating on the markets in the past 5 years. The climax was reached during the frenzy over the spring and summer 2015 (19% or approximately 1 out of 5 companies in our selection listed this year). Right after this, the famous “Hillary tweet” calmed down the sector in September 2015. However, the pace remained sustained in 2016 and 2017, before a sharp decline in 2018 (diverging trend with respect to the US), even more accentuated in 2019 year to date.

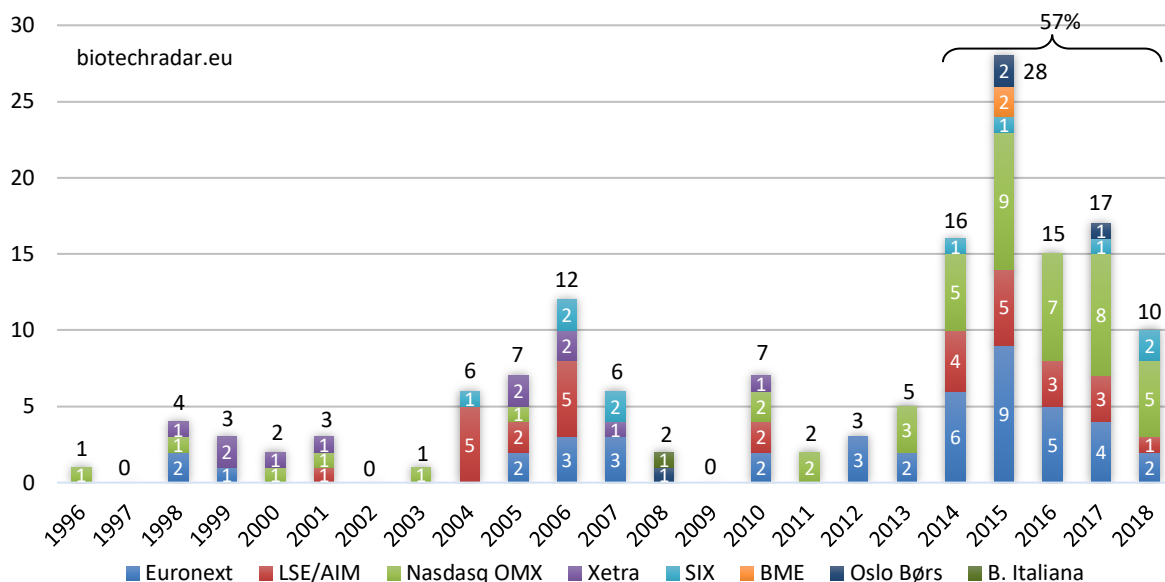


Fig. 4. IPOs/new listings along time, broken down per stock market operator (our universe)

Concerning the dynamics by stock market operator, there was a deluge of IPOs on Euronext between 2014 and 2016, with 7/11 companies floating in Brussels and Amsterdam over this period, 15/44 in Paris over 2014 and 2015. In Stockholm, the pace was also sustained from 2014 to 2018, with 31/41 of the listings over this period. For LSE/AIM, it is a bit more balanced between the mid-2000s and the 2014-2017 period.

Yet, what was seen as a good dynamic in 2014/2015 may now be seen as a concern, or even more, as a mistake. Indeed, more companies on the markets also means more cash needs in the future. Moreover, these cash needs are not linear along the development of the companies, but they grow massively after the proof-of-concept step, reaching a climax on pivotal programs. Therefore, such a large number of IPOs over such a short period of time (4-5 years) basically translated into an imbalance between ask (the public biotech companies) and bid (the investors on the European markets). This is where the problem is today in Europe: the funds available did not grow as much and as fast as the needs. This aspect was, and still is seemingly ignored or not understood by the stock market operators, or at least some of them, who keep inviting new companies to list on their markets (...or how to kill your own business)! In addition, this imbalance was exacerbated by a sentiment reversal in 2015. Of course, many companies try to cope with these needs by trying to partner their assets past proof-of-concept, but this is never a given, and as of today, many companies with so called phase 3-ready assets in their pipeline are in a dead-end case, as they cannot run phase 3 trials by themselves, without a partner to support all or most of the development costs. At the end of the day, the European markets self-regulated markedly: only 5 IPOs took place on Euronext in the past

32 months (0 in 2019 to date & 2 last-minute cancellations in 2018), and there was only 1 IPO on Nasdaq OMX this year (plus 1 listing transfer from Spotlight), far from the 7-8 per year from 2015 to 2017 and even the 5 in 2018. The message seems clear: only the very appealing company profiles will likely succeed on the road to the public markets, or only those with a large institutional/historical investors' backing during the operation (but is it the goal for historical investors?). Otherwise, the message seems pretty clear... Enough (listed companies) is enough (financial burden to bear for the investors).

1.3 New listings/IPOs and M&As in 2018

2018 saw only 10 new listings (**Table 2**), including 6 IPOs (Acacia, MedinCell, Polyphor, AlzeCure, Asarina, Calliditas), 2 listings following an M&A/reverse takeover operation (Oncology Venture from MPI, Okyo from a Cash Shell) and 2 listings without a public offering (Combigene in Stockholm and ObsEva, listed in Switzerland after floating on Nasdaq first). The most active place was Sweden with 5 new listings, followed by Switzerland (2). There was a single event in France, UK and Belgium.

Company	Founded	Stock Exch.	EU IPO Amount (mEUR)/Listing
Polyphor (CH)	1996	SIX Zurich	139.2
Calliditas Ther. (SE)	2004	OMX Stockholm	71.6
Acacia Pharma (UK)	2007	NXT Brussels	40
MedinCell (FR)	2003	NXT Paris	31.4
Alzecure Pharma (SE)	2012	OMX Stockholm	19.4
Asarina Pharma (SE)	2006	OMX Stockholm	15.6
Okyo Pharma (UK)	2018	LSE/AIM London	0 (reverse merger)
Oncology Venture (DK)	2004	OMX Stockholm	0 (reverse merger)
CombiGene (SE)	2014	OMX Stockholm	0 (no offering/transferred from Spotlight)
ObsEva (CH)	2012	SIX Zurich	0 (no offering/listed 1st on Nasdaq in 2017)

Tab. 2. EU IPOs & new listings of European listed biotech companies in 2018 (our universe)

4 companies managed to list on Nasdaq in New York in 2018, of which 3 through an IPO process. The only significant amount raised was for Morphosys (**Table 3**).

Company	Founded	Listing (EU Stock Exch.)	US IPO Amount (mEUR)/Listing
Biofrontera (DE)	1997	2006 (XETRA Frankfurt)	10.4
Morphosys (DE)	1992	1999 (XETRA Frankfurt)	193.1
Tiziana Life Sci. (UK)	2013	2014 (LSE/AIM London)	3.9
Realm Ther. (UK)	2006	2014 (LSE/AIM London)	0 (no offering)

Tab. 3. US IPOs (dual listing) of European listed biotech companies in 2018 (our universe)

On the M&A side (**Table 4**), it was a prolific year (from a European standpoint), with 5 companies who were acquired and subsequently de-listed: Tigenix (Belgium) acquired by Takeda, Ablynx (Belgium) acquired by Sanofi, Wilson Therapeutics (Sweden) acquired by Alexion, TxCell (France) acquired by Sangamo, and Vernalis (UK) by Ligand Pharmaceuticals. For the first 2 names, the

takeovers came after a drug approval (Alofisel and Cablivi, respectively). For Wilson, the tender offer followed good data for WTX 101 now in a pivotal trial in Wilson disease. For the TxCell and Vernalis, it was different. Both companies were facing financial and/or business challenges, so they were opportunistically acquired by 2 US companies.

Acquired Company	Founded	Listing (EU Stock Exch.)	Acquiring Company	Amount (mEUR)	Premium (%)
TiGenix (BE)	2002	2007 (NXT Brussels)	Takeda (JP)	520	81.4
Ablynx (BE)	2000	2007 (NXT Brussels)	Sanofi (FR)	3900	112.3
Wilson Ther. (SE)	2001	2014 (OMX Stockholm)	Alexion (US)	689.6	70.3
Txcell (FR)	2012	2016 (NXT Paris)	Sangamo Ther. (US)	72	177.4
Vernalis (UK)	2003	2012 (LSE/AIM London)	Ligand Pharma. (US)	36.4	16.1

Tab. 4. Acquisitions of European public biotech companies in 2018 (our universe)

Finally, on a wider perimeter, concerning European listed “big pharma”/biopharma companies, Shire (Ireland) was acquired by Takeda for 52.5 bEUR (approximately 60% premium). Karo Pharma (Sweden) was acquired by a fund based in Luxembourg for 580 mEUR (premium about 25%). In 2017, Actelion (Switzerland - not covered) was acquired by Johnson & Johnson for 28.1 bEUR (premium around 77%). Also, in 2017, STADA Arzneimittel, a German pharma (not covered) was partially taken over by a consortium of funds. Another “tranche” of the company was furtherly acquired in 2018 and the company was de-listed early in 2019.

1.4 Development stages by country

The radar plot in **Figure 5** indicates the most advanced development stage of the companies, as of 31/12/2018. For a few cases, we separated the partnered pipeline from the internal developments, thus the mentions “partner” and “internal” associated with some dots (1 dot = 1 company, but 2 dots for each company with split internal/partnered contributions).

The 3 most represented countries, **Sweden, UK, France**, are also the main contributors of early stage companies, gathering **88% of the companies at preclinical/phase 1 stages**. Of note, our definition of “early stage” is “having just reached the proof of concept or before”, as delimited by the red dotted circle. In our view, the Proof-of-Concept (PoC) might be more relevant, as the “phase 2” term might be too vague, without the purpose associated with the “phase 2”. It is not rare to see reports classifying a company that has just started a small phase 2a trial on 30 patients, and another company that has completed a dose-ranging phase 2b on 300 patients, at the same stage, i.e. “phase 2”. The difference between these 2 cases can be important, all other things being equal. So, it is worth seeing if companies are inside or outside the red circle. As always, there are particular cases, e.g. a PoC may be considered as established in a phase 1b or a phase 1[b]/2[a] in oncology, as usually labelled. Also, one could argue on what actually defines a “proof-of-concept”, but we will not go further in this introductory review.

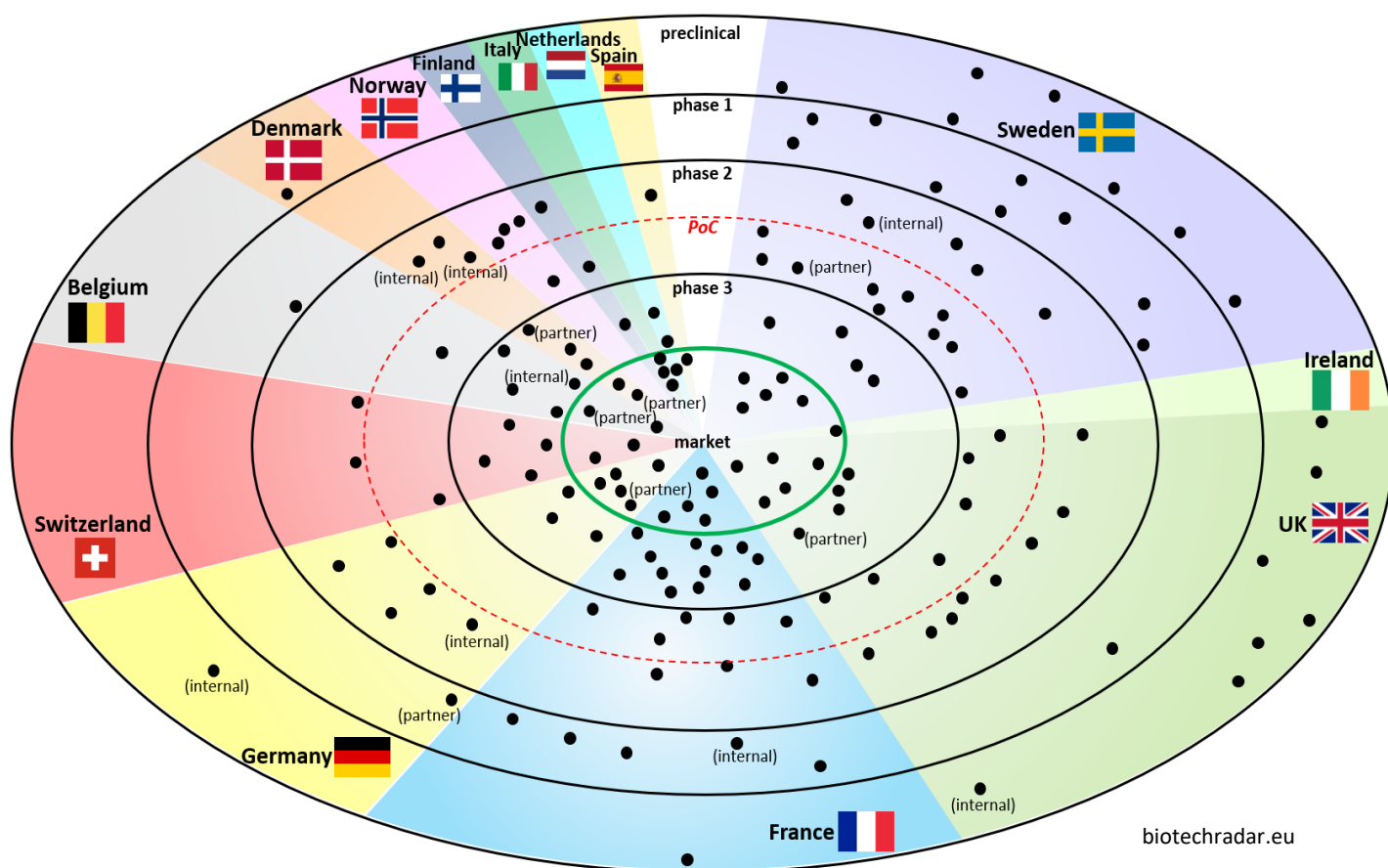
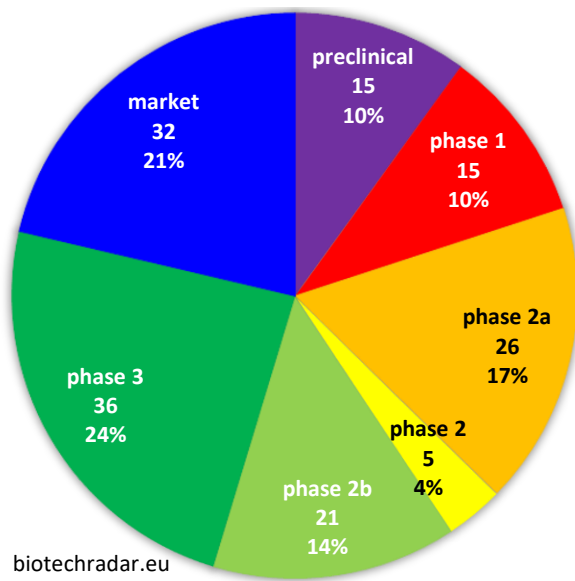


Fig. 5. Radar plot of the European public biotech companies (our universe)

Overall, the number of **companies** that made it to the finish line, **with at least one product generating revenues**, via direct sales or royalty streams is approximately **1 company out of 5 in our selection (32/150)**, as shown on **Figure 6**. The question of whether the marketed products generates strong revenues is another story. **38%** of the biotech companies in our selection can be considered as **“late-stage”** companies, and **27% “early-stage”** ones. 4% can be considered “mid-stage” companies (not early- nor late-stage), while 1 company out of 10 is still at preclinical stage.

Of note, the “phase 1” stage is really a transient stage when put into perspective of the time scale of clinical development, as this is typically the shortest step of all, when everything goes smoothly. Consequently, the proportion of companies in phase 1 should never be really important. Nevertheless, in oncology notably, the phase 1 stage may represent a significant proportion of the global clinical development time (case of 5/15 companies at phase 1 stage in **Figure 7**). Lastly, some companies run both a phase 1a trial in healthy volunteers and a phase 1b in patients to characterize the PK/PD of their investigational drugs more extensively, before moving into phase 2a typically. This is why some “phase 1” stage can last a year or so. This phase 1b step can also be part of a phase 1(b)/2(a). In this case the company stage is classified as phase 2a.

Lastly, some companies may run a pivotal program as soon as phase 2, so before the phase 3 stage (e.g. in oncology and rare/orphan deadly diseases).



The breakdown of companies by country and by development stage is provided on **Figure 7**. We will review more detailed product portfolio and R&D pipeline data in the next sections.

Fig. 6. Distribution of the European public biotech companies by development stage (most advanced project, partnered or internal - our universe)

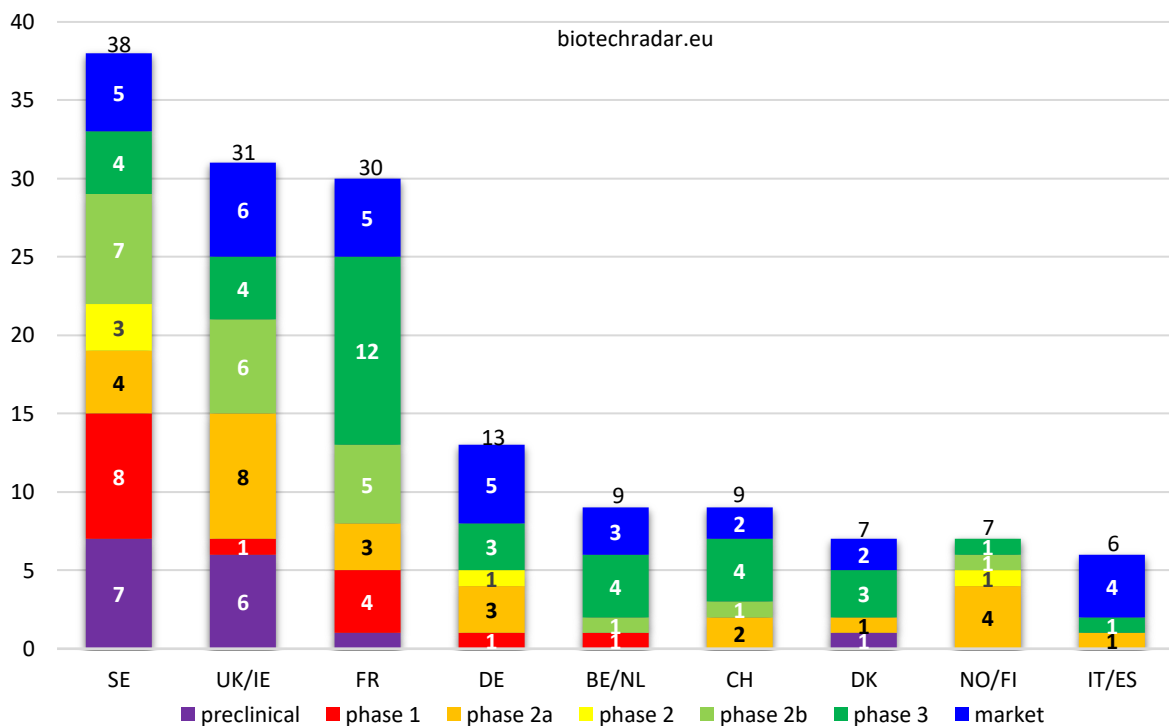


Fig. 7. European public biotech companies by development stage & by country (countries clustered to achieve a minimal number of companies) - highest combined total of late-stage (at least with a phase 2b running) & commercial-stage companies on the left

Finally, looking at the country level (or country clusters that make sense, notably based on geography/similarities), we rendered on **Figure 8** the level of maturity of the respective national biotech sectors, at the end of 2018. Sticking to our early/late-stage definitions, the Belgian/Dutch public sector (n=9 companies) proposes the most mature panel in Europe, along with Switzerland (n=9). Indeed, these 2 clusters look very similar on this chart. The Italy/Spain cluster (“Southern

Europe”) is the subgroup with the highest proportion of commercial stage companies (but n=7 only). Denmark, another small subgroup (n=7) is also well ranked. From the 3 large subgroups (Sweden n=38, UK/Ireland n=31, France n=30), the French sector displays the most advanced companies, proportionally. Sweden is the less mature subgroup in Europe, along with the other Nordic countries, as also depicted on **Figure 5** (radar plot). Especially, when looking at the proportion of companies in phase 3 or higher, we can see there is a gap between the bottom 3 and the rest. Finally, Germany (n=13), displays a good balance, with the second proportion of companies having reached the market.

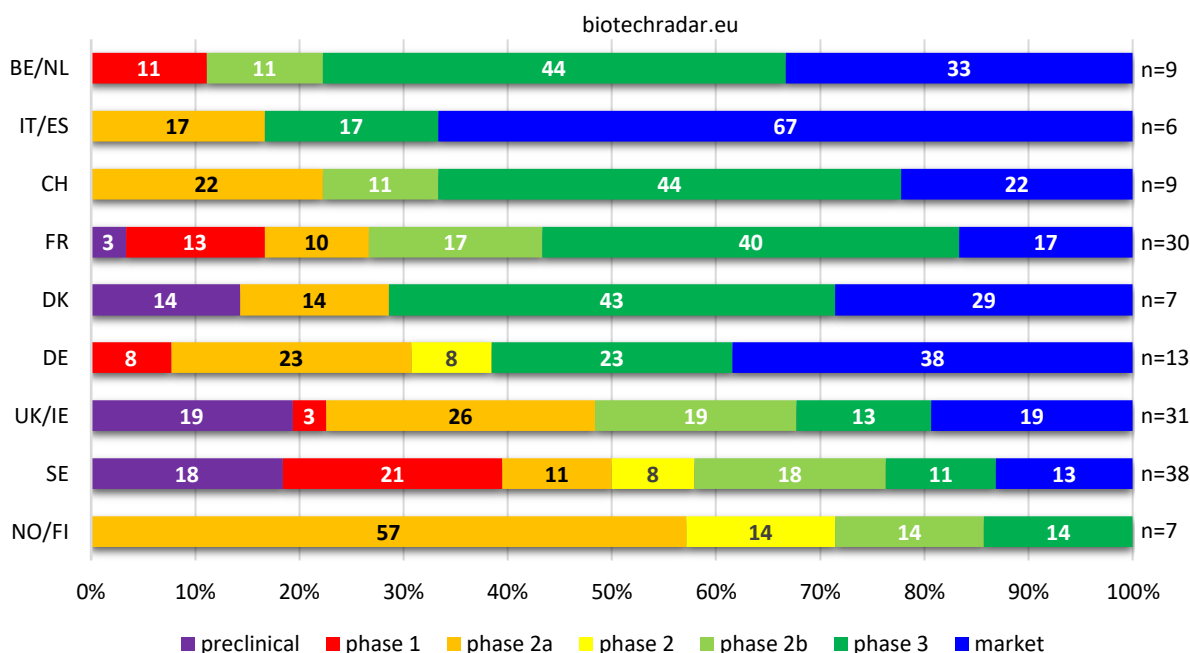


Fig. 8. Distribution (%) of European listed biotech companies by development stage (most advanced program) & by country/cluster - highest combined total of late-stage (at least with a phase 2b running) & commercial-stage companies on top

One should keep in mind there are some important limitations with this representation, especially when it comes to link these data with valuations. First, the most advanced program is not always a good reflect of the richness of a pipeline, both in terms of quantity and quality (e.g. programs more likely to reach the market even if less advanced). Also, it does not indicate anything on the asset NPVs (Net Present Values) in the portfolios. In addition, important distortions may occur with respect to the therapeutic areas. For example, an oncology company in phase 1b already having convincing data may easily have a valuation that is several folds higher than the valuation of a company in phase 2b in a niche indication. In conclusion, as many subgroups have a relatively small number of companies, such distortions may have a significant impact, on top of contributions from outliers.

2. R&D Pipeline & Commercial Products

2.1 Unique product candidates in active clinical development, indications and therapeutic areas

The number of unique product candidates in active clinical development is represented in **Figure 9**, for each country/cluster. These assets are considered to be in active clinical development if they have at least started a phase 1, and if the companies have not declared their development as set on hold/paused/delayed. An asset waiting to be partnered to be developed at a further stage (usually after proof-of-concept) is still considered as active here, although such an event might never occur. However, we set the status on hold anyways if there is no news for a long period. The product candidates having entirely completed their pivotal clinical program and under review for registration are not taken into account here (see dedicated **section 2.2**). Product candidates already approved are not included either, even if their development is pursued in another approved indication (see also **section 2.2**).

The unicity of the candidates is defined with the removal of duplicates from the following categories: indications, territories, targeted populations, formulations. These clinical assets may be developed by the companies alone or with one or several partners, potentially in-licensed and not yet at the registration stage/approved/marketed (even if developed in several indications). The only duplicate cases are when 2 companies in our universe share an asset: in this case, it is counted once for each company, but consolidated again at the country/cluster level if the 2 companies are in the same country/cluster. With our set of criteria, there were **341 unique product candidates in active clinical development** among the European biotech companies in our universe, at the end of 2018 (336 if the assets with shared ownerships among companies in our universe are counted only once).

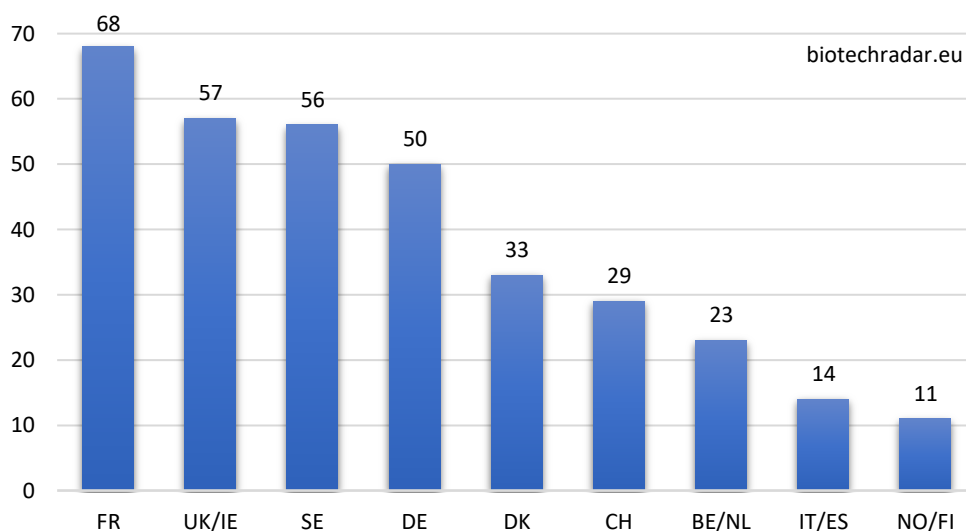


Fig. 9. Unique product candidates in active clinical development, by country/cluster, as of 31/12/2018

Without surprise, the 3 main clusters (France, UK/Ireland and Sweden) are the top 3 contributors. However, as shown on **Figure 10**, UK/Ireland and Sweden globally under-contribute in quantity, as they both have the most important proportion of companies at the preclinical stage (see also **Figure**

8). On the contrary, Germany (thanks to Morphosys and Evotec), Denmark (Genmab), Switzerland (Idorsia) contribute over or well over their respective ratios.

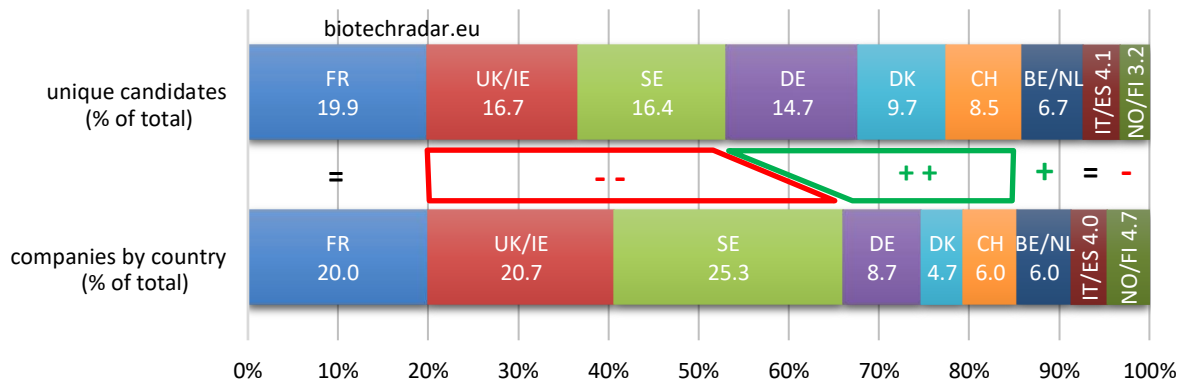


Fig. 10. Distribution (%) of the unique product candidates in active clinical development, by country/cluster

When looking at the absolute numbers by stage and by country (Figure 11), and focusing on the late-stage assets, France is where the highest number of active R&D assets are in late-stage development, particularly in phase 3 (on-going, or completed but not yet filed for registration). The other 2 important clusters complete the podium: the numbers at each stage for UK/Ireland and Sweden are close, with a short edge for the UK in late-stage. Switzerland is also well ranked for the late-stage assets thanks to Idorsia (4 unique assets in phase 3 for this company alone). **57 unique assets were in phase 3 at the end of 2018.**

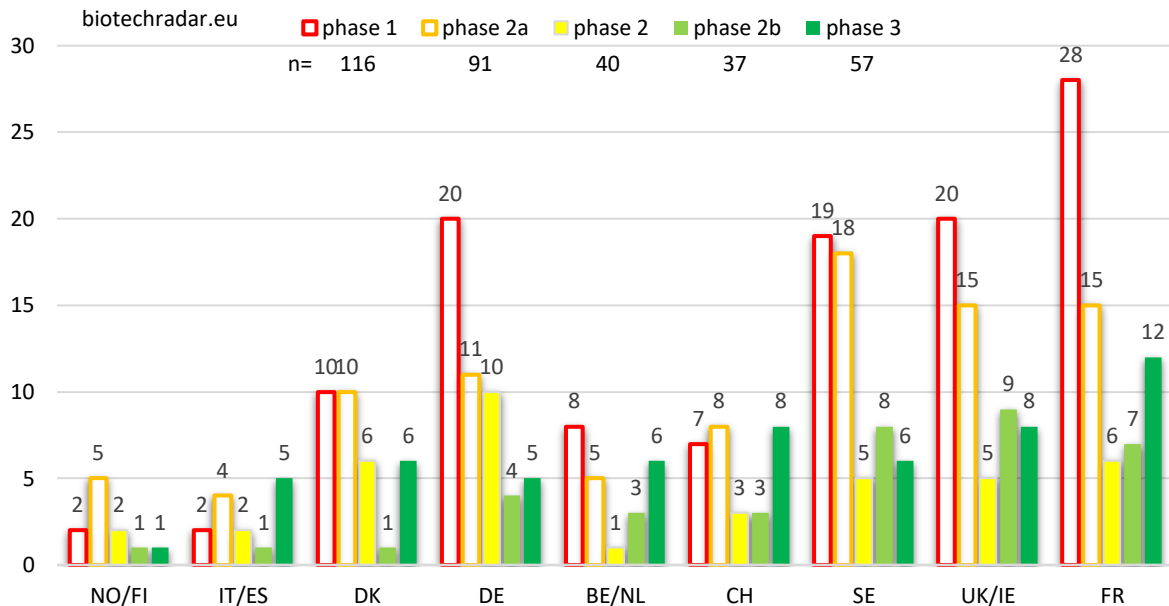


Fig. 11. Number of unique product candidates in active clinical development (n=341), by clinical stage and by country/cluster - highest number of late-stage assets on the right (late-stage assets=phase 2b, phase 3, phase 2/3 and also “phase 1/3” as usually called by companies developing biosimilars/generics)

Germany has an abnormal number of unique product candidates at the phase 1 stage. This is due to 2 companies, Morphosys and Evotec, which are 2 of the most important R&D powerhouses (mainly in the frame of partnered programs) in our European biotech universe, if not the 2 most important

ones. Morphosys has built an important partnered pipeline over the past 2 decades, and the business model of Evotec is to deliver phase 1-ready candidates for their customers, so in fact, no real surprise here. Still on early-stage assets, Sweden and the UK have a similar number of product candidates both at the phase 1 and phase 2a/PoC stages. However, as seen on **Figure 8**, Sweden has relatively more phase 1-stage companies than the UK. This illustrates the fact that in Sweden, the phase 1 assets are more lead assets whereas in the UK, they are almost only follow-on assets within broader and/or more advanced pipelines.

Germany also has the highest number of mid-stage phase 2 assets, owing this position to a high number of oncology assets at this stage, from 4SC AG and Morphosys.

Of note, France is ranked in the TOP 3 at each development stage, without any special outlier. Knowing that more than 70% of the French biotech companies reached either the commercial stage or a late stage (**Figure 8**), this means that the 60% of early stage assets (**Figure 12**) are usually follow-on R&D projects as well, complementing at least one other later-stage asset. We may do one remark concerning the lack of outliers among the French biotech landscape. This is interesting on one hand because the potential is globally evenly spread over the landscape. But on the other hands, outliers are signs of success(es). So far, the French sector is still looking after THE company with a blockbuster in the pipeline, able to address a large population, and likely assisted by a Top 10 Big Pharma on its way to vertical integration: in other words, a good success story. In contrast, Belgium/Netherlands do not look particularly strong on **Figure 11**, but at least 2 of the late-stage assets are already worth billions (filgotinib and efgartigimod, 2 assets with a “pipeline-in-a-product” profile, with an option as well for cusatuzumab, and others if approved). At the end of 2018, in terms of market cap, Galapagos alone was worth more than the 30 French biotech companies in our universe listed in Paris...

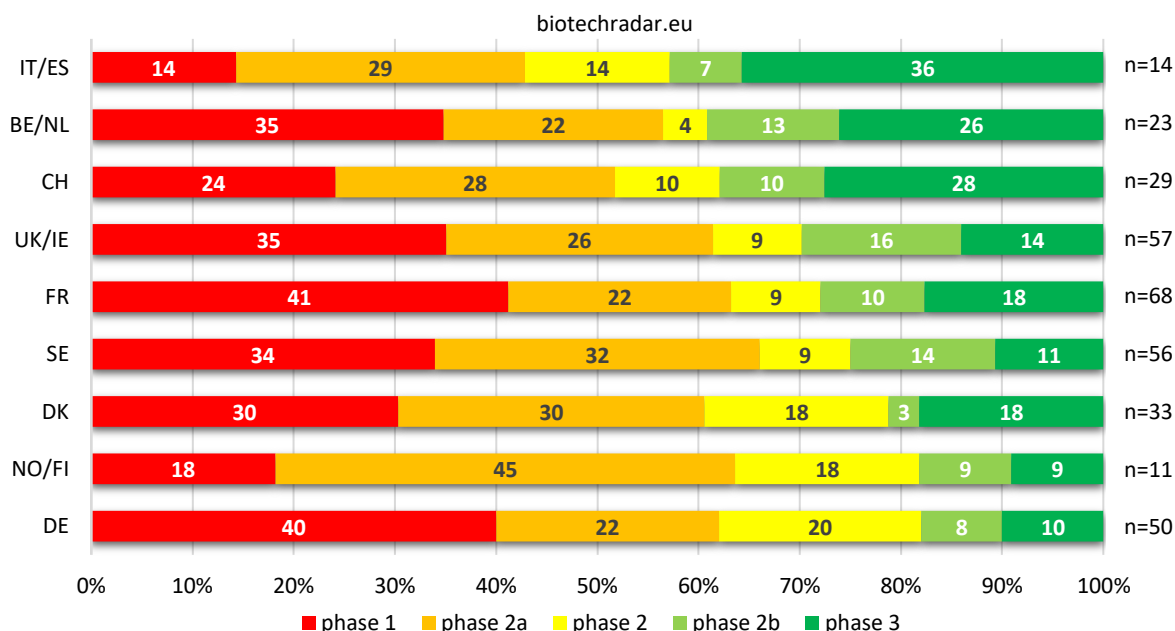


Fig. 12. Distribution (%) of the unique product candidates in active clinical development, by clinical stage and by country/cluster - highest proportion of late-stage assets on top

The distribution of the unique assets in active development broken down by clinical stage is represented on **Figure 12** for each country/cluster. While the picture in the Top 3 is almost the same versus the distributions of companies ranked by most advanced development stage from **Figure 8**,

the rest of the ranking is entirely reshuffled. Italy/Spain indeed takes the first place to Belgium/Netherlands but the proportion in the Top 3 is very close, all around 40%, with a 10% gap on the fourth place. The main differences concern the UK/Ireland (+3) and Germany (-3). For the UK, the fact that we removed the preclinical assets -and thus the 6 preclinical companies- make the contribution of the clinical-stage companies look much better (the same reason applies for Sweden, +2 in the ranking). For Germany, the explanation was mentioned above: the contributions in early-stage assets of Evotec and Morphosys dilute the later-stage part. The same dilution operates for Denmark, where Genmab and Saniona contributions at the Proof-of-Concept stage make the national sector move down by 2 places.

Overall, **all these R&D assets were addressing 271 unique indications at the end of 2018**, with many assets addressing several of them.

Like everywhere else in the world [16-17], oncology, just reported as having taken over from cardiovascular diseases for the leading cause of death worldwide [18], is the most pursued area, with roughly one fourth of all the indications (**Figure 13**). Two areas come next, with 15%: immunology/inflammatory diseases/allergy (including autoimmune diseases) and neurology/psychiatry to which we attach toxicity management/rescue, as well as addiction and anesthesia/sedation. These 3 areas include slightly more than half of the indications (56%). Another small quarter is composed of ophthalmology/otorhinolaryngology, infectious diseases and endocrine/metabolic diseases, each between 6 and 8%. The last quarter is very fragmented, with 9 areas between 1 and 4%. Of note, infectious diseases, a huge unmet need worldwide because of the antimicrobial resistance concerns, gather 6% of the indications, especially in the UK and Switzerland. In contrast, only 4% of the candidates in active development address cardiovascular diseases, the formerly leading cause of deaths in the world until 2017 [18].

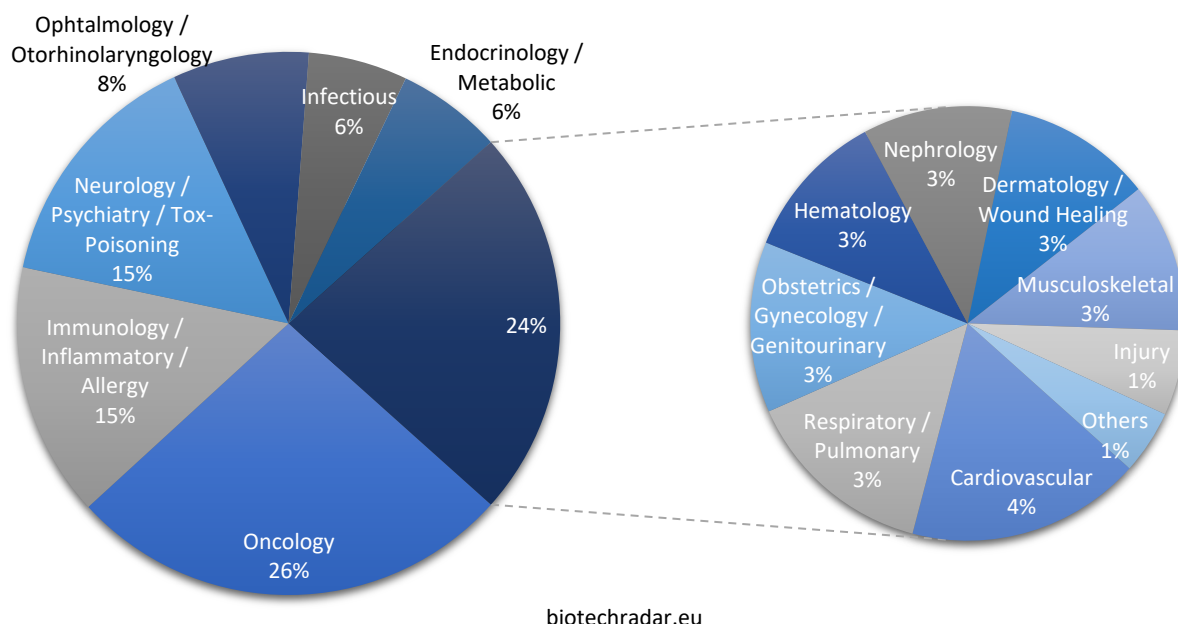


Fig. 13. Therapeutic areas addressed by unique R&D product candidates in active clinical development by the European listed biotech companies (our universe)

Rare diseases (as listed on rarediseases.org and orpha.net, with a prevalence cut-off we have set around 100 thousand cases in the US, so not aligned with the EU/US Orphan Drug Designation criteria), a focus of many companies nowadays, represent approximately 17% of these indications, and are spread among a broad panel of therapeutic areas (11). Three therapeutic areas have a significant edge on the others in this specific therapeutic segment: neurology (20%), endocrine & metabolic diseases (18%) and immunology (16%).

2.2 Product candidates in registration and commercial products

As shown previously on **Figure 6**, 21% of the European public biotech companies have reached the commercial stage, either by themselves, via a partner, or an in-licensing deal. The contributions by country in terms of marketed products are shown on **Figure 14** (no duplicate due to approvals in many indications or with several formulations).

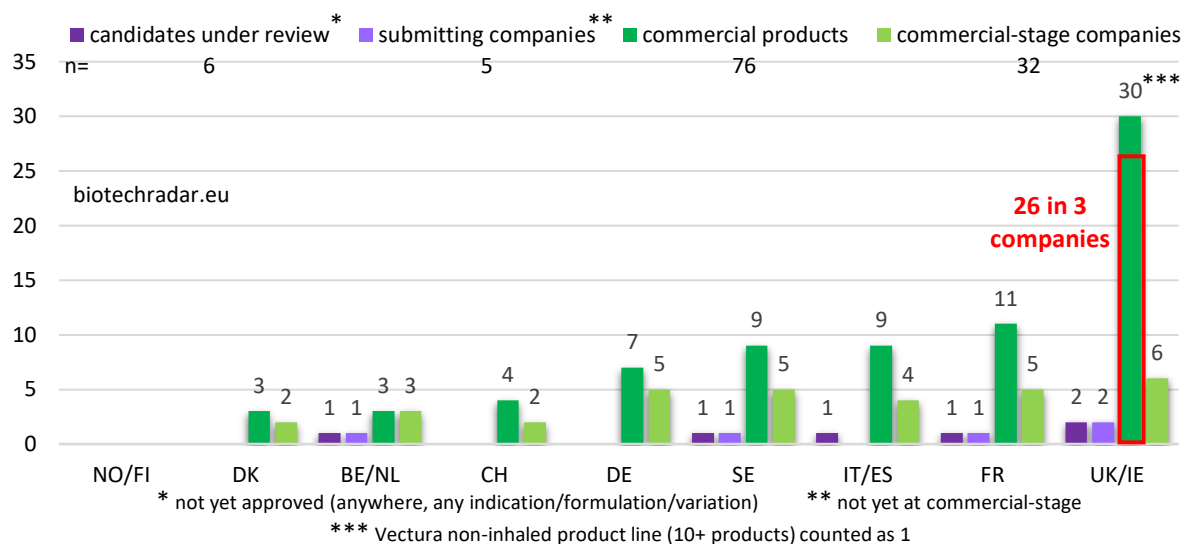


Fig. 14. Product candidates in registration/commercial products, newly-submitting/commercial-stage companies by country/cluster, as of 31/12/2018

Indivior, Allergy Therapeutics and Vectura pull the numbers up for the UK. Overall, the number of companies at the commercial stage at the end of 2018 is quite homogeneous between UK/Ireland, France, Italy/Spain, Germany and Sweden, each with 4 to 6 companies. This is also the case for the number of commercial products, excluding UK/Ireland. The “Southern Europe” cluster and Germany perform well on this metric once again, when compared to the number of companies in these respective countries. There was a **total of 76 unique commercial products as of 31/12/2018**, including 3 products regulated as medical devices. Additionally, 2 products from 2 acquired companies (caplacizumab/Cablivi from Ablynx now Sanofi, and darvadstrocel/Alofisel from Tigenix/Takeda) were formally approved in 2018 (not taken into account in these figures).

Still on **Figure 14**, 5 pre-commercial-stage companies were waiting for an approval/certification at the end of 2018: Nanobiotix (France) for NBTXR3 (Hensify - regulated as a medical device, granted CE marking in 2019), Acacia Pharma (UK) for APD421 (BARHEMSYS - second CRL issued by the US FDA), Motif Bio (UK) for iclaprim (CRL issued by the FDA), Paion (Germany) for remimazolam (still

under review), and Kiadis (Netherlands) for ATIR-101 (also still under review). Finally, we also add CB-17-01 (Methylene Blue MMX - CRL confirmed by the FDA in November 2018 but still filed in Europe in Q1 2019) from Cosmo to the 5 candidates just mentioned. Overall, **6 unique product candidates -never approved before- were at the registration stage at the end of last year**, with a review ongoing somewhere in the world.

The therapeutic areas addressed by the few companies with several products are particularly well weighted in the overall distribution (**Figure 15**). Neurology (and associated areas) is the leading area among the approved products, with almost one fourth of the share. Another half of the share is composed of infectious diseases, respiratory/pulmonary diseases, immunology and oncology, with 12-14% for each of this areas. Dermatology (along with Wound Healing) and Ophthalmology/Otorhinolaryngology represent approximately 10% of the therapeutic areas.

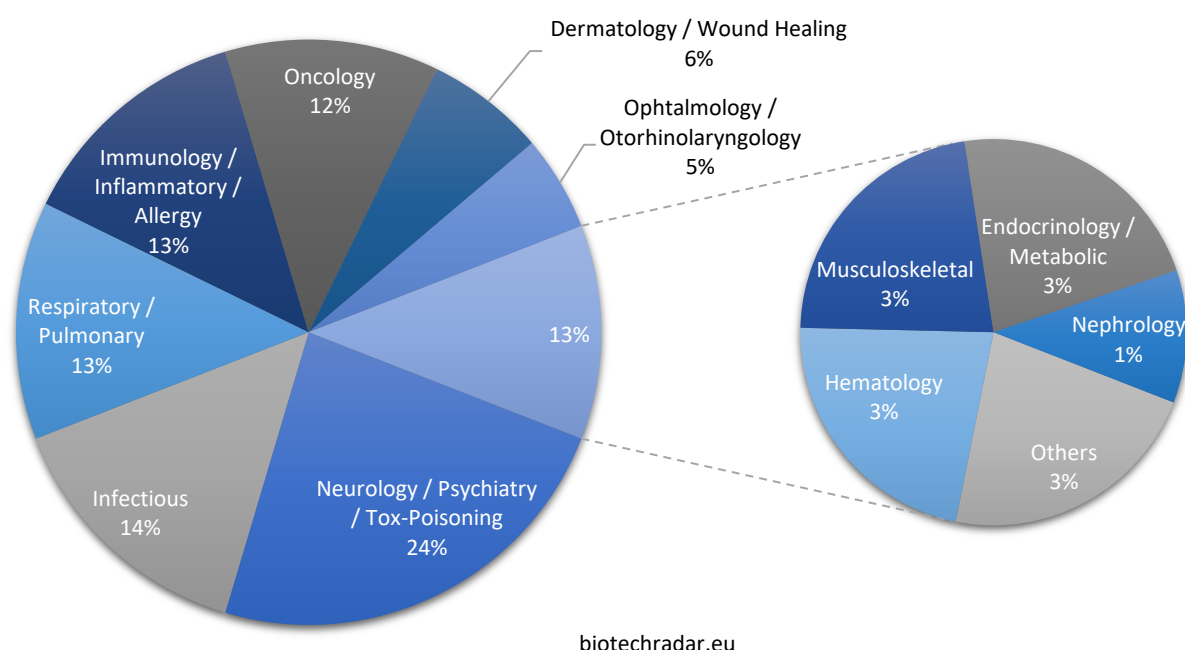


Fig. 15. Therapeutic areas addressed by the 76 commercial products approved from our European biotech universe (1 area only per product), as of 31/12/2018

Only 3 products (4%) could be deemed to address a rare disease. A number likely to grow in the coming years though, as it is identified as an industry megatrend [17].

2.3 Assessing the full pipeline breadth: R&D programs in active clinical development

In this last part dedicated to the pipeline of the companies, we broaden the scope to all the indications addressed (only those in active development). We will define an “R&D program” as a unique combination of: a product candidate, a target indication (it can be a group of indications, e.g. Solid Tumors), a target population (e.g. pediatric / adult / elderly, a biomarker-based selected population, or a broader “all-comers”). The pivotal programs composed of 2 or more clinical trials are therefore counted only once. We also include the trial run by partners, as well as some

Investigator-Initiated Studies (IIS), also called Investigator-Sponsored Trials (IST), but only if the trial is run in an indication that is not already studied by the companies or their partners. The products may also be approved in other indications. Finally, as described before, we assign a program to both companies when the ownership is shared through a licensing or a collaboration scheme, but it is consolidated at the country/cluster level again, in the case where both the licensing company and the licensee belong to the same country/cluster.

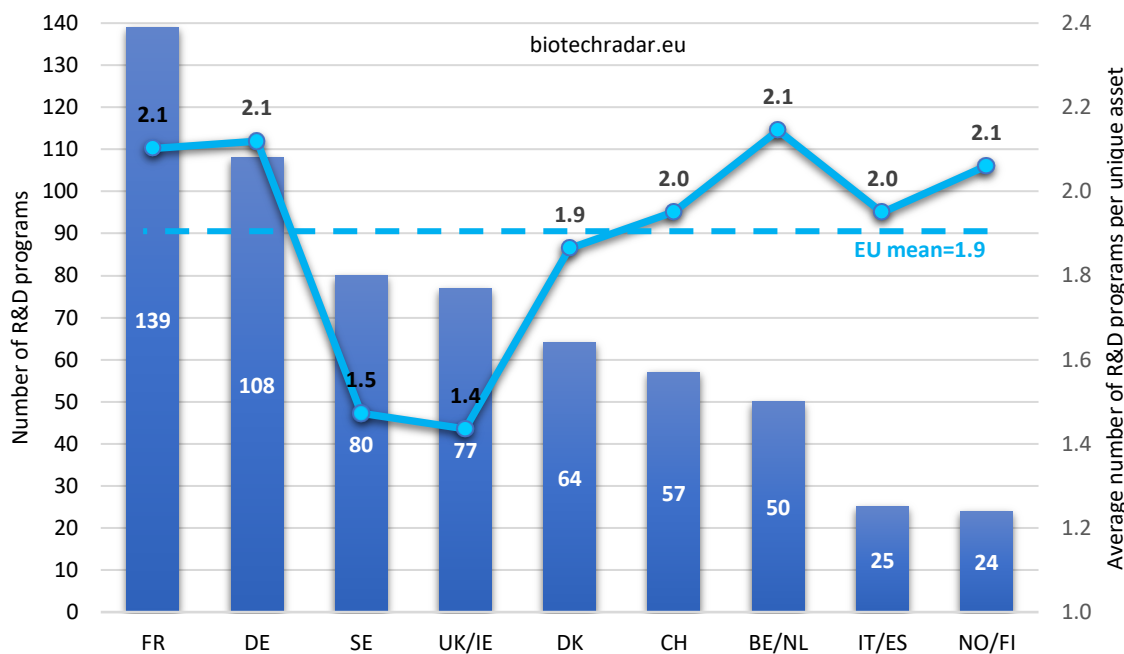


Fig. 16. R&D programs in active clinical development by country/cluster (624 in total), and average number of R&D programs per unique product candidate, as of 31/12/2018

The distribution of the 624 R&D programs in active development is shown on **Figure 16**, for each country/cluster. The average number of R&D programs per unique asset is also provided. Looking at the absolute numbers, Germany shines by jumping from the fifth to the second position, as compared to **Figure 9** (unique assets), owing this jump to the very broad -but mostly partnered- pipeline of Morphosys. Overall, the ranking is close to the one established for the unique assets. Sweden and UK/Ireland switch their positions, but the data are almost the same for both countries.

The picture changes a little bit when comparing how many R&D programs are derived per unique asset, on average (also **Figure 16**). With very few variations among the countries/clusters, one asset is actively developed simultaneously in 2 clinical programs, on average. This metric calls for additional insights though: the average number of R&D programs for a unique asset is actually driven by a small percentage of “pipeline-in-a-product” drugs. More concretely, **53 unique product candidates out the 341 unique product candidates (or 16%) were investigated in 3 or more programs**, revealing the presence of 2 distinct populations of assets: those investigated 1 or 2 programs (**average of 1.1 active R&D program/product candidate - 84% of the product candidates**), and the so-called “pipeline-in-a-product” drugs (**3 or more programs – 16% of the product candidates**) found to be investigated in **5.8 active R&D programs, on average**. Galapagos drives the numbers up for Belgium thanks to the large number of phase 2a of filgotinib. The average number of programs per asset is pumped up by phase 1 trials for Norway/Finland, thanks to BergenBio’s bemcentinib, investigated in several cancer

types. Finally, the average number of phase 3 programs per asset is particularly high in Germany, thanks to Biofrontera’s Ameluz and guselkumab (Tremfya) from Morphosys/JNJ.

We will not show the figure similar to **Figure 10**, as the picture would typically be the same for the contributor’s balance for R&D programs, which makes sense. Though, in comparison, the contributions of Germany, France and Belgium/Netherlands grow up to 47.6% of the R&D programs versus 41.3% of the product candidates, thus compensating for share losses of Sweden and UK/Ireland (25.1% of the R&D programs versus 33.1% of the product candidates).

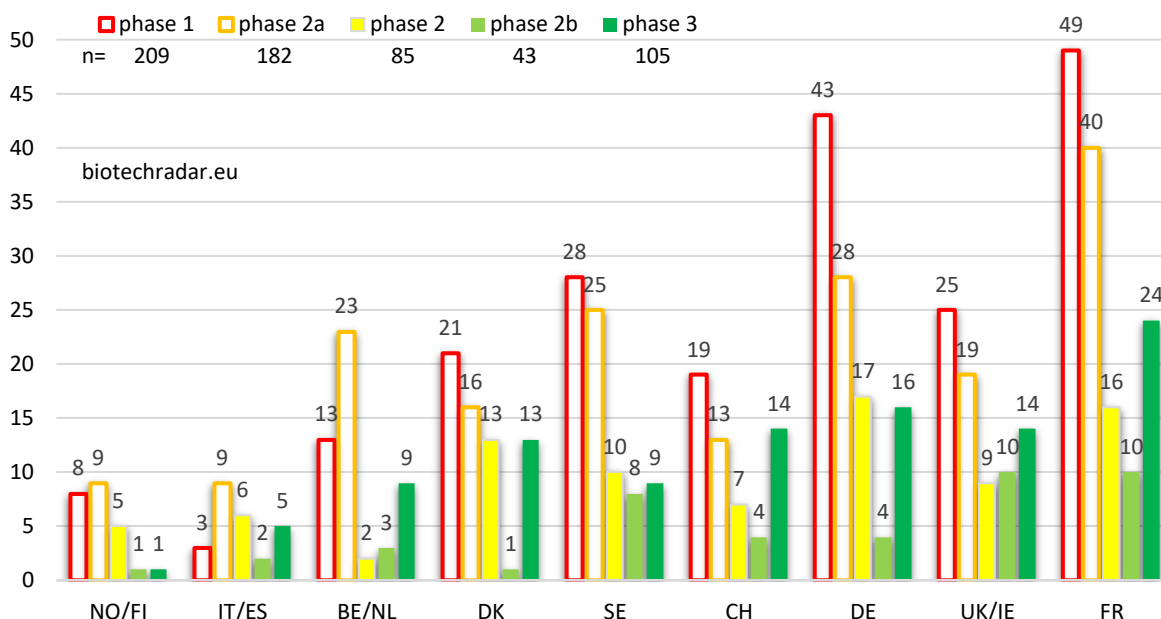


Fig. 17. Unique R&D programs in active clinical development, by clinical stage and by country/cluster (624 in total) - highest number of late-stage assets on the right (see notes from Fig. 11)

The 624 unique R&D programs are broken down by country/cluster and by development stage on **Figure 17**. We still represent the early-stage bars unfilled for an improved visualization of the data. Germany’s numbers are boosted in this ranking compared to **Figure 11** (unique R&D assets). Indeed, Morphosys, the largest contributor in our universe with more than 60 unique programs in active development (alone and partnered), contributes a lot to this leapfrog (+3). On the contrary, Sweden and Belgium/Netherlands both go down by 2. For Sweden, this is explained by what we have described before, i.e. younger and less advanced companies, with narrower pipelines versus Germany and Switzerland. Concerning Belgium/Netherlands, the contribution of Galapagos does not manage to offset the effect of a lower number of companies in the cluster. Mid-stage-wise, Germany, France and Denmark are the top contributors, with a very large majority of programs in oncology. On the early-stage side, like for product candidates, France tops the ranking for R&D programs, with an even extended lead over the other 2 main countries/clusters (Sweden and UK/Ireland). Germany almost competes with France with twice as less companies, again mostly thanks to Morphosys, and to Evotec to a lesser extent. There were **105 unique phase 3 programs at the end of 2018**.

The French biotech sector, ranks first or second at all development stages, reflecting both the ability of the French companies to deliver product candidates intended to be developed in several programs, in line with the standards (around 2 programs per candidate), which is less the case in the

UK and Sweden. Germany shines in this ranking despite a lower number of companies, but this outperformance mainly lies into the contributions of 1 or 2 companies.

Finally, closing with the relative composition of the aggregated active R&D programs at country/cluster level (**Figure 18**), the first point is that the proportions at each stage are relatively similar to those reported for the unique assets (**Figure 12**). For the R&D programs from phase 1 to phase 3, the percentages are 31 / 31 / 15 / 7 / 17% on **Figure 18**, respectively. On **Figure 12**, these are 30 / 29 / 12 / 10 / 18% for the same stages. There is a slight decline overall at the late-stage, rounded to -5%, compensated by +2% at the mid-stage and +3% at the early-stage.

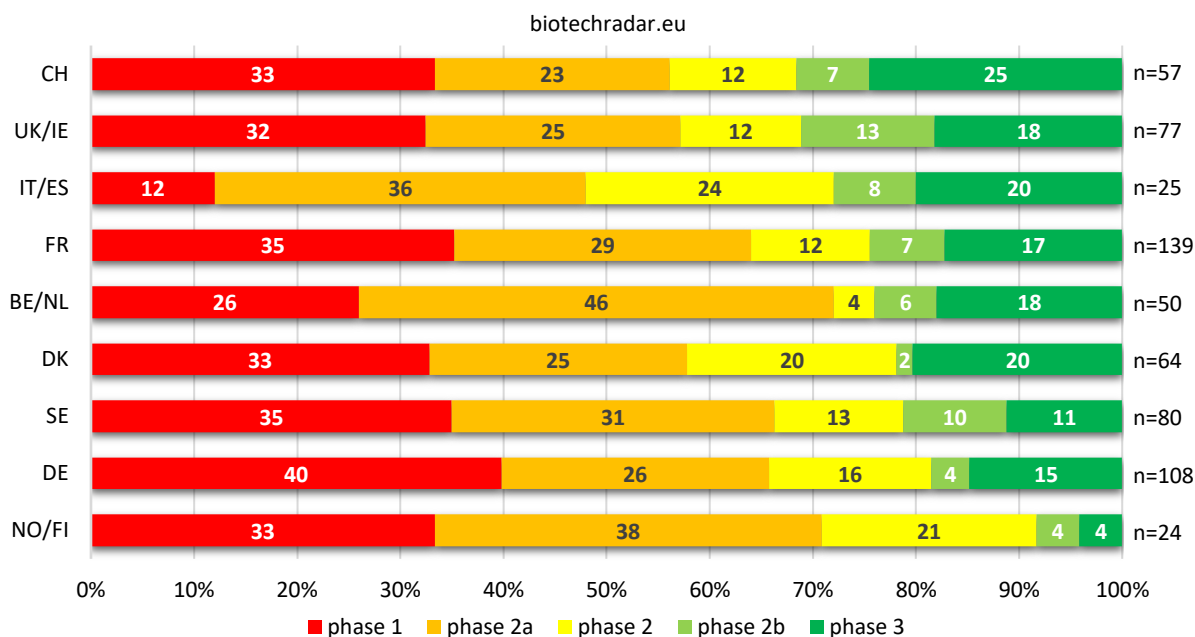


Fig. 18. Distribution (%) of the R&D programs in active clinical development, by clinical stage and by country/cluster - highest proportion of late-stage assets on top

At another level, the variations by country can be quite important. For example, Belgium and Netherlands rank down by 3 versus **Figure 12**, because the high proportion of late-stage assets is finally diluted by the high number of early-stage programs (in particular by the phase 2a trials of filgotinib in several indications). The same applies for Norway/Finland (-1), where several phase 1 programs impacts the proportion of the late-stage programs. For the “Southern Europe” cluster (-2), the late-stage assets are also diluted, but by mid-stage programs (phase 2). Denmark (+1) is the only country with a significant increase of the proportion of late-stage programs, compared to the proportion of product candidates at the same stage. Germany (+1) and UK/Ireland (+2) are around neutral for their ratio of late-stage programs compared to the late-stage product candidates. Switzerland (+2), Sweden (-1) and France (+1) are both moderately diluted at the late stages. Switzerland takes a short lead on UK/Ireland, with the highest proportion of late-stage assets. Overall, the gap at the late stages between the different countries/clusters is narrowed. On **Figure 12**, the proportions of late-stage assets ranged between 18 and 43%, versus 19 and 32% on **Figure 18** for the proportions of late-stage of R&D programs, discarding Norway/Finland’s massive dilution.

To conclude with the pipeline data, the absolute numbers indicate that France offers the largest potential of value creation, along with the UK/Ireland, as of 31/12/2018. Germany, with only half less

companies, also has an attractive profile, with a deep pipeline, but dominated by one outlier. Switzerland and Denmark look alike in absolute, but the Swiss sector tops it in relative. Sweden is in-between these 2, due to a less mature landscape. Belgium/Netherlands do not seem especially great by the absolute numbers, but the comments at the end of the **section 2.1** also apply here. Italia/Spain figures are low quantitatively, but are on the higher range qualitatively. Lastly, Norway/Finland, like Sweden, present a pretty early stage offer that asks to gain in maturity.

3. Market data

3.1 Market capitalization

At the end of 2018, the total market capitalization of the 150 European public biotech companies in our selection amounted to 43.8 bEUR (billion euros). To put this total valuation into perspective, it represents approximately one fourth of Novartis or Roche, or half of Sanofi. Not apple-to-apple comparisons obviously. The **Figure 19** below indicates the market capitalization of each company, sorted from the lowest to the highest. Note the logarithmic scale on the Y-axis. The overall shape may be explained by the natural spread over various development stages, indications and by the valuation models themselves (including “leveraged” model inputs along the development of the products, like the discount rates, probabilities of success, and potentially the cost of capital). A log transformation (not shown) on the distribution tends to indicate a log-normal distribution.

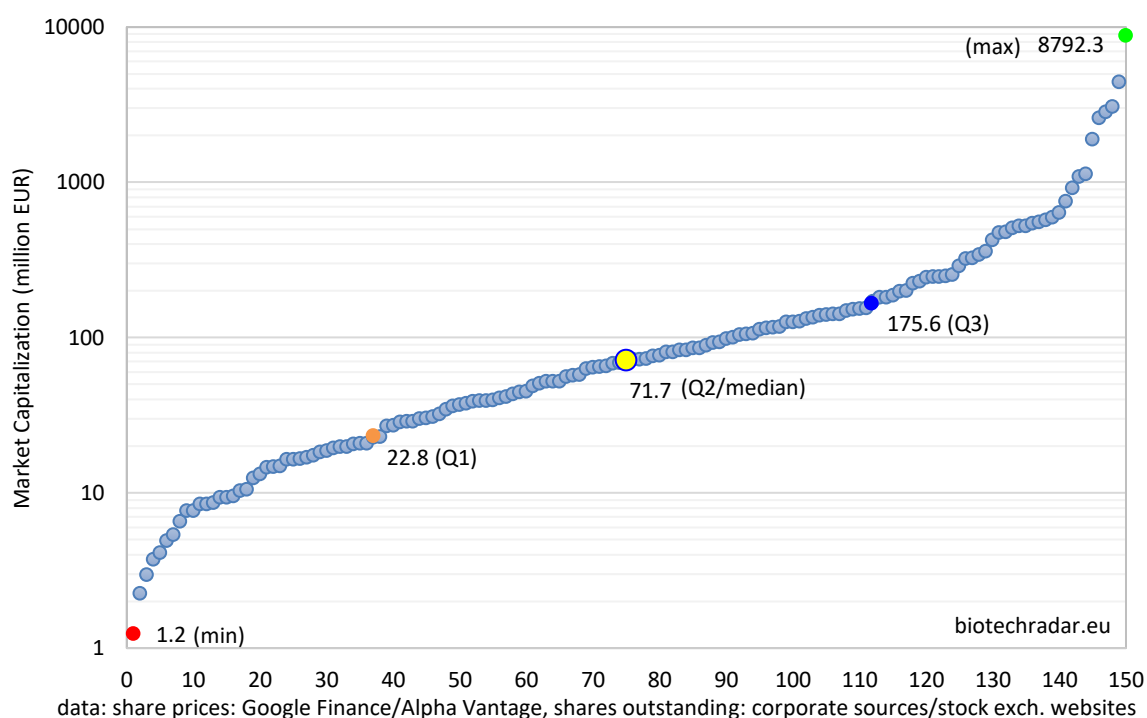


Fig. 19. Market cap of 150 selected European public biotech companies (our universe)

As we aimed at building a selection with a managed heterogeneity, through our inclusion and exclusion criteria, it seems this goal is globally achieved. An exponential trend engulfs approximately 80 to 87% of the companies, depending on your tolerance for what you call “a good fit” ($R^2 \sim 0.99$ in

both cases anyways). The valuations globally follow a continuum over this exponential trend -which can be viewed as an oxymoron-, even if there are 2 tails on each side, with an accelerating trend upwards on the top end, and downwards on the bottom end. The valuations are spread over almost 4 orders of magnitude (4 logs). **The median market cap at the end of 2018 was only 71.7 mEUR.** One should have in mind that December was a really bad month for stocks in general (the worst since 1931 for the DJIA & the S&P500, with a clear impact in European markets at this period).

The main statistical data on market cap distribution can be found in **Table 5**.

Total (million EUR)	43786.6		
10th percentile	9.4	50% of total market cap	5 companies
1st quartile	23.9	75% of total market cap	20 companies
median	71.7	90% of total market cap	52 companies
3rd quartile	178.8	95% of total market cap	74 companies
90th percentile	522.3	3% of the companies	
		13% of the companies	
		35% of the companies	
		49% of the companies	

Tab. 5. Market capitalization data, n=150 European biotech companies, as of 31/12/2018 (million EUR)

The same shape as **Figure 19** could be found for biotech companies listed on the Nasdaq markets in New York (no data/chart provided). A log transformation would also tend to indicate a log-normal distribution, however the distribution after transformation exhibits a slight asymmetry of the peak towards higher values. Even if the perimeter might not be 100% equivalent to our European universe with respect to our inclusion/exclusion criteria, we would find a **median market cap of 194.2 mUSD out of 503 selected companies listed on Nasdaq** (including foreign companies). With an exchange rate of 1.1482 USD for 1 EUR at the end of last year, this leads to a **ratio of circa 2.3-fold between the median market cap on Nasdaq versus European markets**. Attention, this **DOES NOT** automatically translate into "European public biotech companies are undervalued compared to the US". The **total valuation of this Nasdaq selection**, excluding the "Big Pharma" companies (NYSE) and the Top 7 companies on the Nasdaq (Amgen, Gilead, Biogen, Shire, Celgene, Regeneron) **was approximately 391 bUSD, or 9-fold the total market cap of our European universe**.

Additional market data at the end of 2018 are presented in the **Table 6** below, by country/cluster:

	EU	FR	BE/NL	DE	CH	UK/IE	SE	DK	NO/FI	IT/ES
market cap (bEUR)	43.8	4.3	9.3	6.5	3.6	3.0	4.6	10.0	0.5	2.0
market cap (%)	100	9.8	21.1	14.8	8.2	7.0	10.5	22.8	1.2	4.5
median market cap (mEUR)	70.0	97.3	198.1	85.5	175.0	30.1	41.8	115.8	36.1	183.9
average perf. 2018 (%)*	-17.0	-22.0	+16.5	-32.4	-38.0	-46.3	+16.0	-17.3	-41.7	-33.9
median perf. 2018 (%)*	-29.3	-27.5	+2.0	-35.6	-39.2	-52.3	+0.8	-3.1	-37.5	-41.9
n=	150	30	9	13	9	31	38	7	7	6
* (incl. 5 de-listed co.) N=	155	31	11	13	9	32	39	7	7	6

Tab. 6. Market capitalization by countries (clustered) & 2018 consolidated stock performances

The total market capitalization, as of 31/12/2018, was 43.8 bEUR, a decline of 7.2 bEUR compared to 31/12/2017 (51.1 bEUR), of which 2.2 bEUR from acquired/de-listed companies (150 companies at the end of 2018, compared to 147 at the end of 2017). This corresponds to a variation of **-14.5%** on the grand total (**-10.6%** by excluding the de-listed companies). This variation was offset by a

contribution for 1.0 bEUR of newly-listed companies during 2018. Excluding both newly and de-listed companies in 2018, the variation was **-12.7%** on the total value year-over-year.

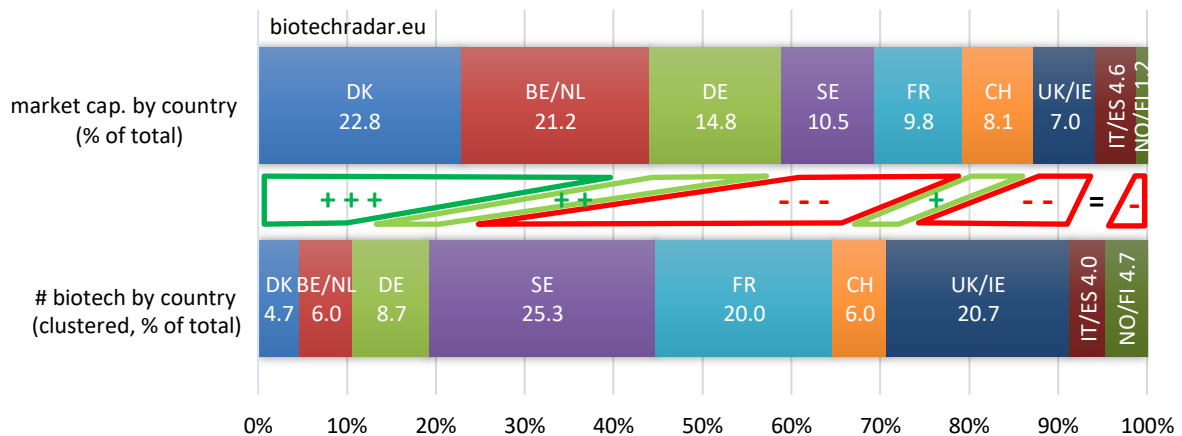


Fig. 20. Distribution of the total market cap, by country/cluster

On **Figure 20**, Denmark and Belgium/Netherlands are overweighed in the total market valuation, thanks to Genmab and Galapagos/Argenx, respectively (see also the Top 20 European listed biotech companies at the end of the 2018, on **Table 7** below). Germany and Switzerland are slightly over-represented when comparing the market cap contribution of these countries with respect to their contribution in the number of companies. The 3 largest countries/clusters (Sweden, France, UK/Ireland) are therefore underweighted, with globally a higher proportion of early-stage companies for Sweden and UK, as already reviewed in the pipeline section of this review. Moreover, other factors might explain these low figures for the French and British biotech sectors, like the high clinical failure rate for UK in 2018, or companies globally delivering below investors' expectations for France. On top of that, one may add the financing concerns, weighing on many companies.

The same picture is rendered on the distribution of the market cap by stock exchange (**Figure 21**).

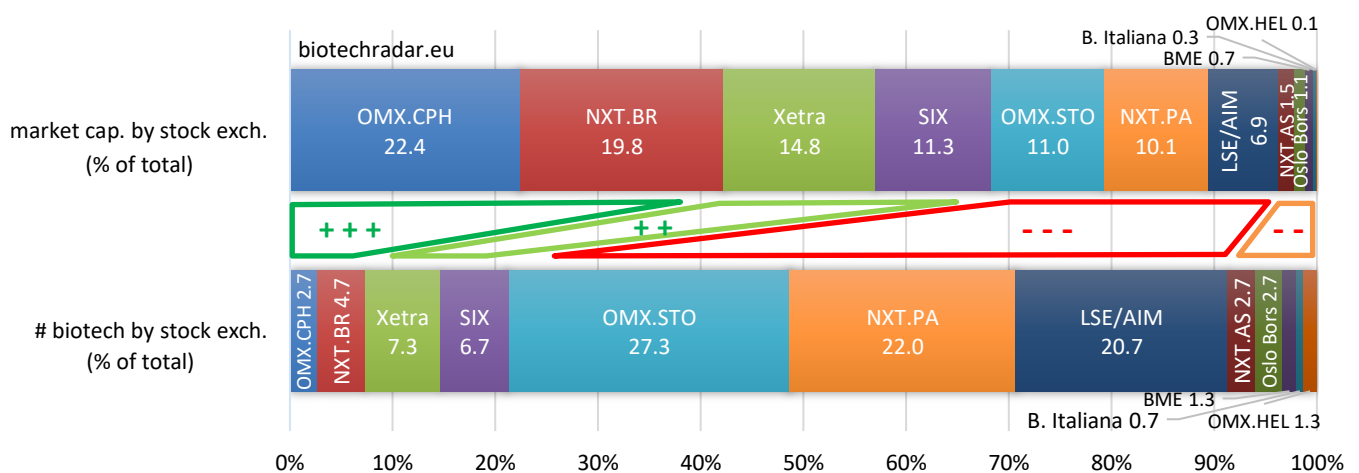
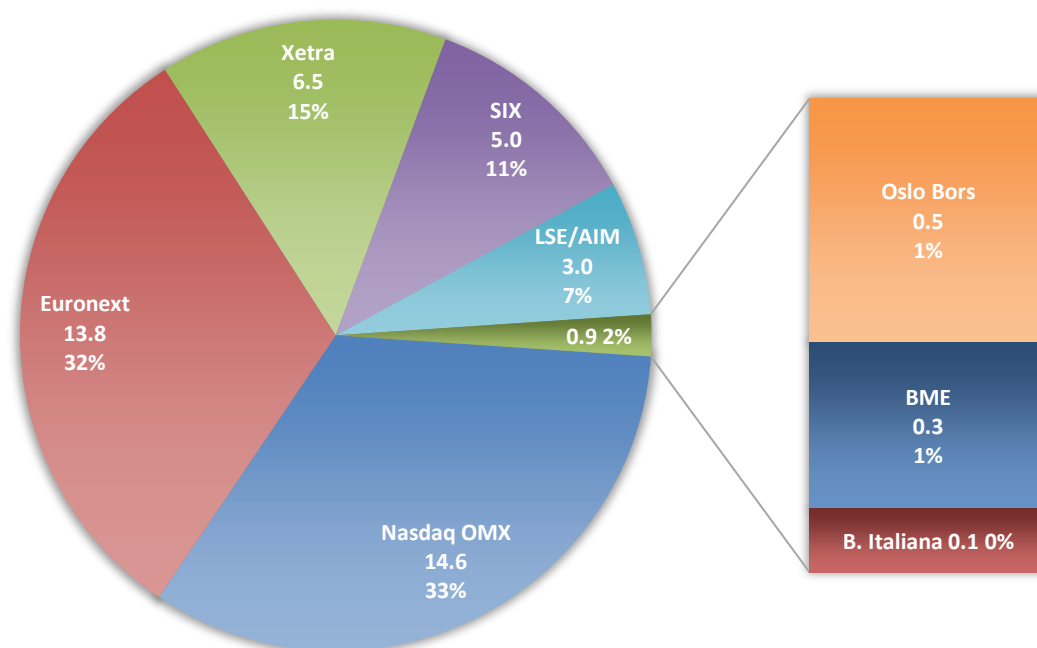


Fig. 21. Distribution of the total market cap, by stock exchange

However, when consolidated by stock market operator (**Figure 22**), **2 main groups dominate the biotech field: Nasdaq OMX and Euronext, each representing one third of the value.** Then come Xetra and SIX, in the overweight zone compared to the number of listings hosted. **LSE/AIM clearly**

lags. Given that Oslo Børs is now part of the Euronext group, the 2 leaders get even closer in terms of number of companies, but also of market cap. Given the large discrepancies observed (**Figure 21**), one may sum it up this way: the quantity in the offer does not make the quality of the offer.



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Fig. 22. Distribution of the total market cap, absolute (bEUR) & relative (%), by stock exchange platform

The Top 20 companies by market capitalization at the end of 2018 is listed on **Table 7**:

	Company	Market Cap (mEUR)
1	Genmab (DK)	8792
2	Galapagos (BE)	4388
3	Argenx (BE)	3061
4	Morphosys (DE)	2832
5	Evotec (DE)	2586
6	Idorsia (CH)	1887
7	Cosmo Pharma. (IT)	1125
8	Hansa Biopharma (SE)	1087
9	Indivior (UK)	911
10	Mithra Pharma. (BE)	753
11	Cellectis (FR)	635
12	BioArctic (SE)	594
13	Oncopeptides (SE)	570
14	Bavarian Nordic (DK)	552
15	Genfit (FR)	541
16	Oxford Biomedica (UK)	520
17	Vectura (UK)	519
18	ObsEva (CH)	506
19	Innate Pharma (FR)	475
20	Pharming Group (NL)	469

Tab. 7. Top 20 European listed biotech companies, n=150 listed in Europe, as of 31/12/2018

Only 8 companies made it to the “billion euro” biotech club at the end of 2018 (9 in USD). One may notice the absence of any French company in the Top 10, and the global under-representation of France and UK in general in this ranking. As a comparison, **84 companies out of the 503 selected companies on Nasdaq (similar but slightly wider perimeter) had a market cap superior to 1 bEUR (89 in USD).**

3.2 Stock performances

2018 was a negative year for stocks in general. In Europe, the main indexes were down 11% for CAC40 (FR), 18.3% for the DAX (DE), 18.5% for the BEL20 (BE), 12.5% for the FTSE100 (UK) and 14.3% for the EUROXTOXX 50. In the US, the Down Jones lost 5.6% versus 6.5% for the S&P500, while the Nasdaq Composite declined by 3.9%. The Japanese NIKKEI also lost 12.1%.

In the US, the biotech ETF XBI (equal-weighted) lost 15.5%, and the IBB ETF lost 9.7%, which is worse than the main indices mentioned before. The conclusion is the same for European biotech stocks, when compared to the main European indices. Indeed, the small caps compartment was not likely to outperform in a context where the market sentiment was globally negative (trade war, US Fed rates) and even more in Europe (lack of growth and structural reforms, Brexit, despite a supportive ECB policy over the past years). Overall, the full-year **2018 stock performance for the 155 biotech companies in our list (150+5 de-listed) was -17% on average, or -29% for the median** (see previous **Table 6**), which is consistent with the “High Beta” profile of this subsector. Despite a very tough end of year on the markets, 2 countries/clusters managed to end in positive territory, for both their average and median performances (barely positive for the latter): Belgium/Netherlands, and Sweden (note the spread between the mean and median performances). **UK biotech stocks lost roughly half of their value on average, but more impressively also on the median, with a long list of clinical trial failure.** Denmark did relatively well, as compared to France, Germany, Switzerland, the Nordics and the Southern Europe.

The list of the FY18 stock performances >50% can be found in **Table 8.a**, while those < -50% are shown in **Table 8.b**. Out of the 5 de-listed companies, given that 4 of them were acquired, their performances were consistent with the application of a premium.

Oasmia jumped after the European approval of Apealea (nanoparticle formulation of paclitaxel), Bioarctic soared thanks to the surprise success of BAN2401 phase 2b in Alzheimer (run by Eisai/Biogen). The speculation over Cantargia’s anti-IL1RAP brought the stock to new highs, while IRLAB Therapeutics capitalized on the successful proof-of-concept of IRL752 in Parkinson’s. Only 7 companies more than doubled.

Company	Country	FY18 %
Oasmia Pharma.	SE	+249.2
BioArctic	SE	+215.4
Wilson Therapeutics *	SE	+129.1
Cantargia	SE	+121.9
IRLAB Therapeutics	SE	+120.3
Ablynx *	BE	+117.2
Diamyd Medical	SE	+104.1
Mithra Pharmaceuticals	BE	+94.9
Xintela	SE	+88.1
TiGenix *	BE	+83.5
Active Biotech	SE	+73.0
Quantum Genomics	FR	+69.5
TxCell *	FR	+67.5
Oncopeptides	SE	+64.3
Argenx	BE	+62.2
Oxford Biomedica	UK	+59.8
Innate Pharma	FR	+56.6

Tab. 8a. Best FY18 stock performances (> +50%), * = acquired companies, n=17

For the decliners, FIT Biotech managed to realize the extraordinary performance to divide its stock price by more than 40-fold, because of financing issues and a terrible snowball effect from convertibles, all combined with a low liquidity on the stock. These troubles eventually killed the company who went into administration at the beginning of 2019. Immupharma plunged on the pivotal trial failure of Lupuzor. Faron collapsed on its lead Traumakine phase 3 failure in ARDS. A1M delayed the entry in clinics of their first candidate, while Summit Therapeutics crashed on vanished hopes in Duchenne Muscular Dystrophy. The following reasons (at least one for each company) drove the decliners' stock performance listed in **Table 8.b**: clinical failures, financing issues, regulatory setbacks, delayed plans, legal issues, strategic decisions, deceptive sales, etc...

British biotech companies represent 35% (17/49) of the decliners' list, highlighting a sobering year (with a notably bad impact for the Woodford fund into 2019). France is also well represented among the Top decliners, with 11 companies (22%). There is no Danish company in this ranking (but low number of companies in Denmark).

Company	Country	FY18 %	Company	Country	FY18 %
FIT Biotech	FI	-97.6	4D Pharma	UK	-70.4
Immupharma	UK	-93.1	Erytech Pharma	FR	-66.2
Faron Pharma.	FI	-92.9	Acacia Pharma	UK	-64.4
A1M Pharma	SE	-90.1	Biophytis	FR	-63.8
Summit Therapeutics	UK	-88.0	AB Science	FR	-58.4
Hybrigenics	FR	-87.1	Lysogene	FR	-57.9
Mologen	DE	-85.9	Targovax	NO	-57.9
Diurnal Group	UK	-85.6	Neovacs	FR	-56.5
Noxxon Pharma	DE	-83.9	Destiny Pharma	UK	-56.5
Midatech Pharma	UK	-83.3	Pharma Mar	ES	-56.0
Realm Therapeutics	UK	-82.4	Tiziana Life Sciences	UK	-55.9
ValiRx	UK	-81.3	Kancera	SE	-55.5
Santhera Pharma.	CH	-81.3	ASIT biotech	BE	-55.1
Cyxone	SE	-77.0	co.don	DE	-53.8
Probiodrug	DE	-76.1	NeuroVive	SE	-53.7
DBV Technologies	FR	-74.7	Polyphor	CH	-53.1
ReNeuron	UK	-74.3	Avacta	UK	-52.3
Cerenis Therapeutics	FR	-74.3	Celyad	BE	-52.1
Crossject	FR	-73.9	Allergy Ther.	UK	-51.8
Shield Therapeutics	UK	-73.3	Newron Pharma.	IT	-51.6
Silence Therapeutics	UK	-73.0	Karessa Pharma	SE	-51.6
Sensorion	FR	-72.7	Camurus	SE	-50.8
Indivior	UK	-72.5	Nicox	FR	-50.6
Annexin Pharma.	SE	-70.9	Medivir	SE	-50.4
Redx Pharma	UK	-70.7			

Tab. 8b. Worst FY18 stock performances (< -50%), n=49

The waterfall plot in **Figure 23** recapitulates the full-year 2018 stock performances of the 150 biotech companies in our selection, plus the 5-delisted companies during 2018. With the colors, one can easily see the outperformance of Belgium/Netherlands and Sweden, and the underperformance of UK/Ireland. For France, the pattern is quite dichotomic, with a group between -50 and -75%, and another one between +10 and +70%. A similar pattern can be observed for Denmark, but with a much lower number of companies and in other ranges. The Annus Horribilis of the British biotech sector, with bad news all year long, can also be visualized on **Figure 24**, representing the heatmap of the stock performances throughout the year. As the markets mostly ended on their lows, the information out of this figure might be a bit redundant with the waterfall plot. The strong second half of the Swedish sector (also on **Figure 25**), the strong start of Belgium/Netherlands, and the tough last quarter of France are the most recognizable patterns. The impact of the market correction occurring in Q4 can also be spotted.

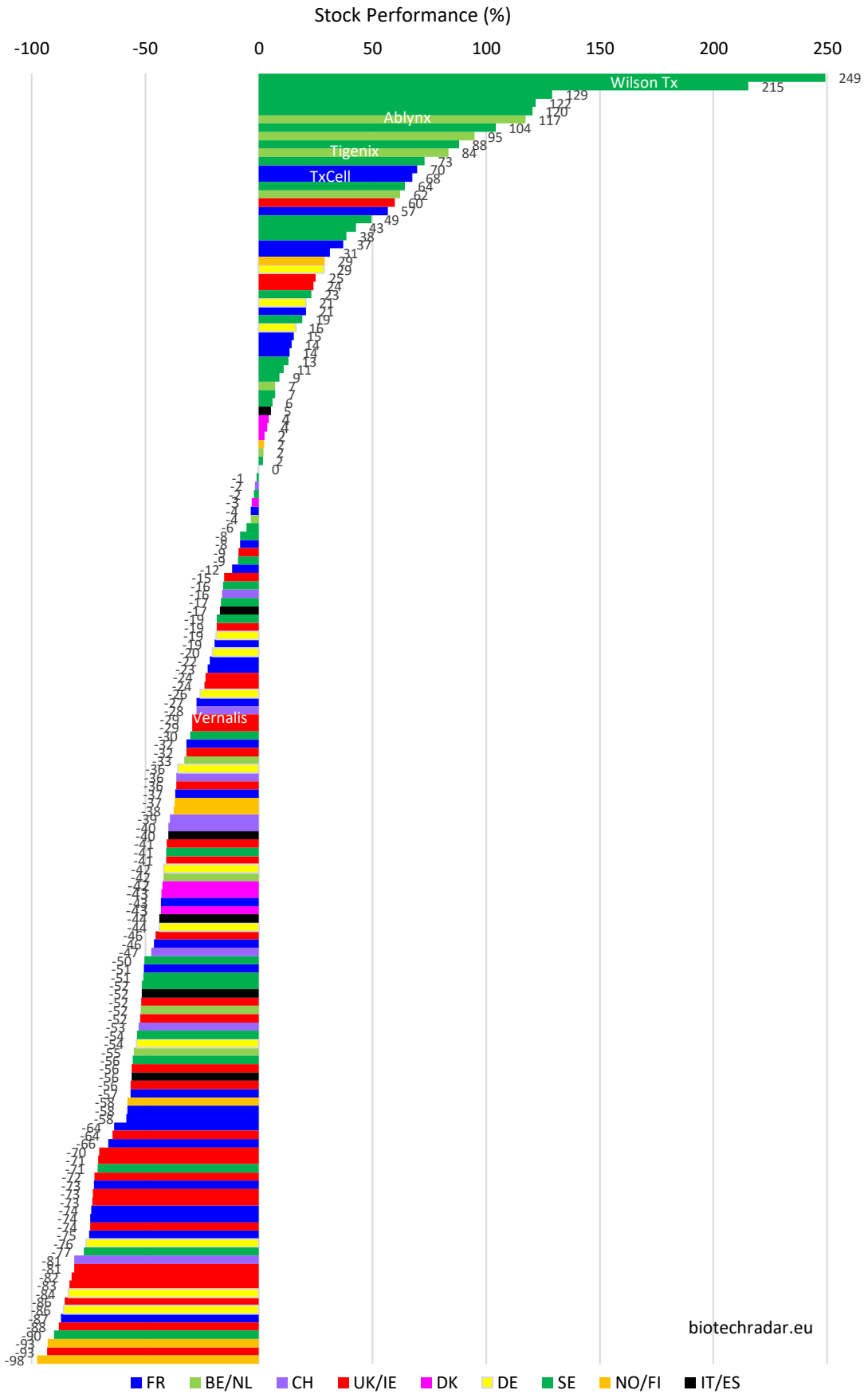


Fig. 23. 2018 stock performance (%) of 155 European listed biotech companies, by country/cluster, including 5 de-listed stocks (Wilson Therapeutics, Ablynx, Tigenix, TxCell, Vernalis)

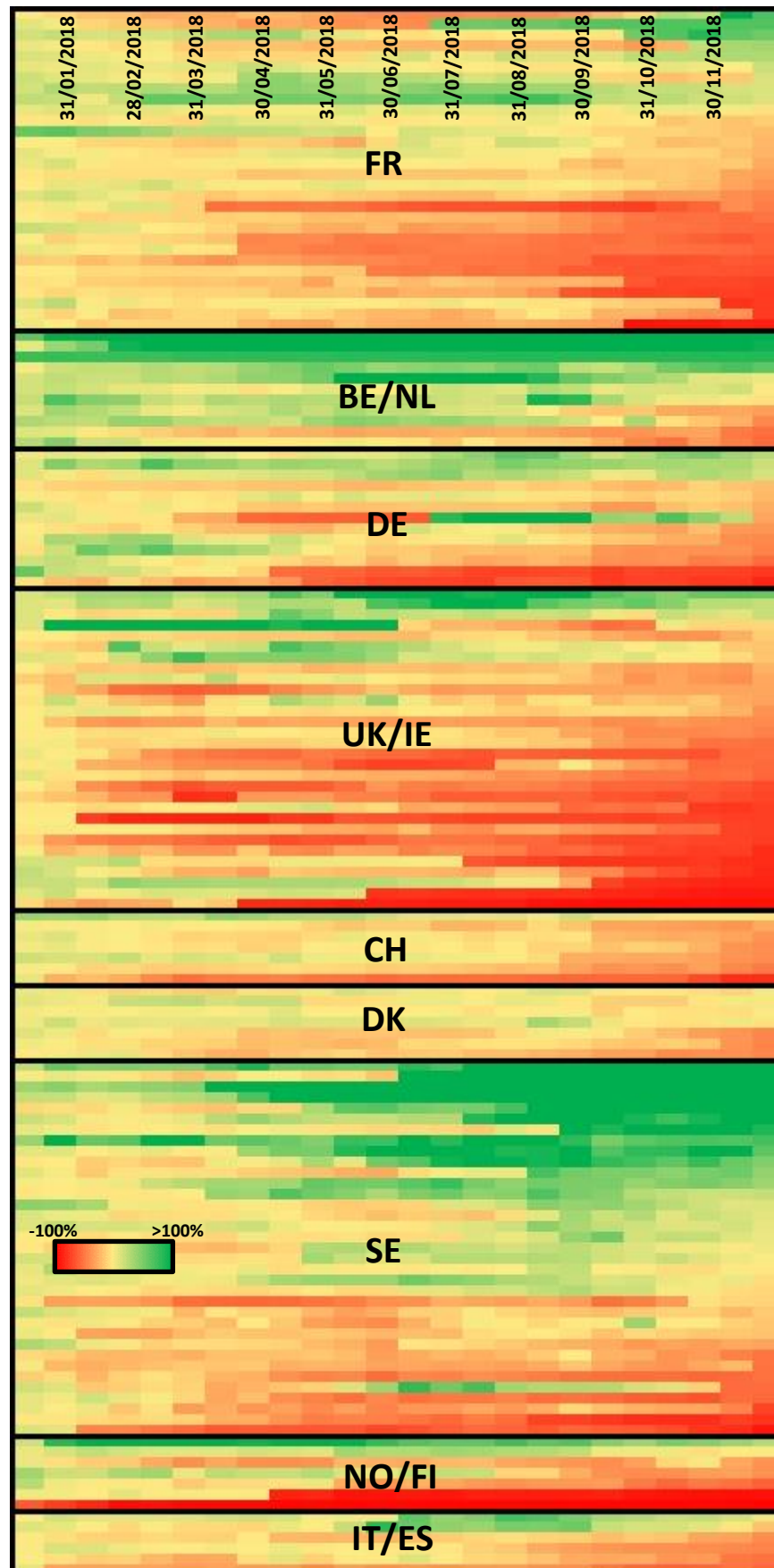


Fig. 24. Heatmap of the stock performance (%) of 155 European listed biotech companies during 2018, by country/cluster, color code: red -100%, green +100% and more

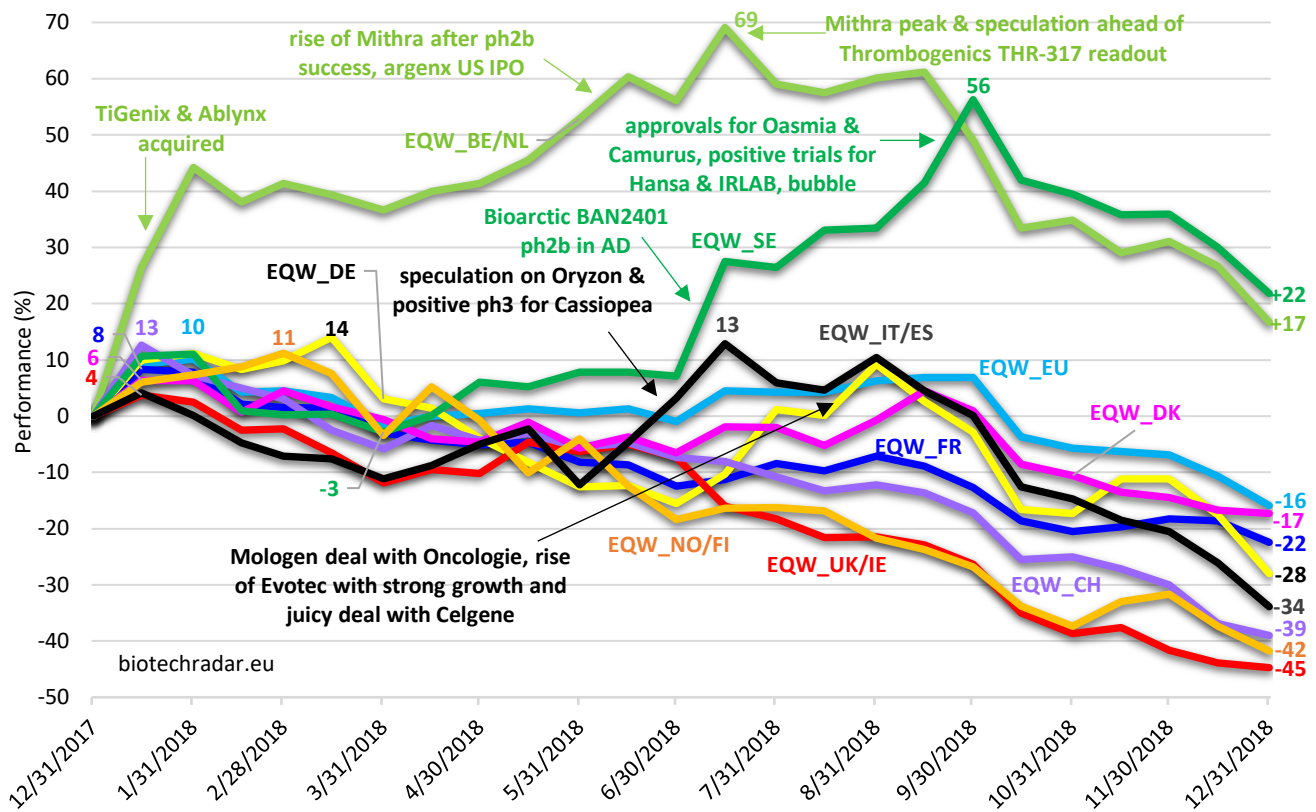


Fig. 25. 2018 performance (%) of each equal-weighted indices, for Europe and the 9 countries/clusters

The performances are also shown on **Figure 25** in the forms of equal-weighted indices, for Europe and for each by country/cluster. Thanks to the periodic runup caused by the JP Morgan Annual Healthcare Conference each year, early in January, 4 out of the 9 countries/clusters peaked at that time before fading down almost all year long. The global European index also peaked in January, driven by the 2 acquisitions on TiGenix and Ablynx. Norway/Finland and Germany also peaked a bit later during the first quarter 2018. Belgium/Netherlands went basically flat after a strong kickoff (2 buyouts mentioned before), and peaked in July thanks to Galapagos (deal for MOR106). Sweden had a mostly neutral trend before the surprising phase 2b results of BAN2401 in Alzheimer’s Disease in July. Once initiated, this good momentum was kept with drug approvals for Oasmia and Camurus, a positive outcome in a patent litigation for Orexo, positive trials for Hansa or IRLAB Therapeutics, and bubble-like speculation moves on many small Swedish companies like Cantargia, Xintela, Diamyd, Corline, Active Biotech, among others. Germany and Italy/Spain managed to transiently rebound before the general drop of stocks during the Fall and December. All the indices were down in Q4 2018, mainly due to macroeconomic factors.

The 2018 performance of our European biotech index, in both equal-weighted and cap-weighted versions, is compared with 2 reference US (or mostly US) biotech ETFs on **Figure 26**, the SPDR S&P BIOTECH “XBI” (equal-weighted) and the iShares Nasdaq Biotechnology “IBB” (cap-weighted). For the cap-weighted index, we limited the contribution of the largest weights to 8%, which is more or less the largest holdings in the “IBB” ETF. For simplicity’s sake among other things, there was no rebalance applied during the year, nor any float-adjust.

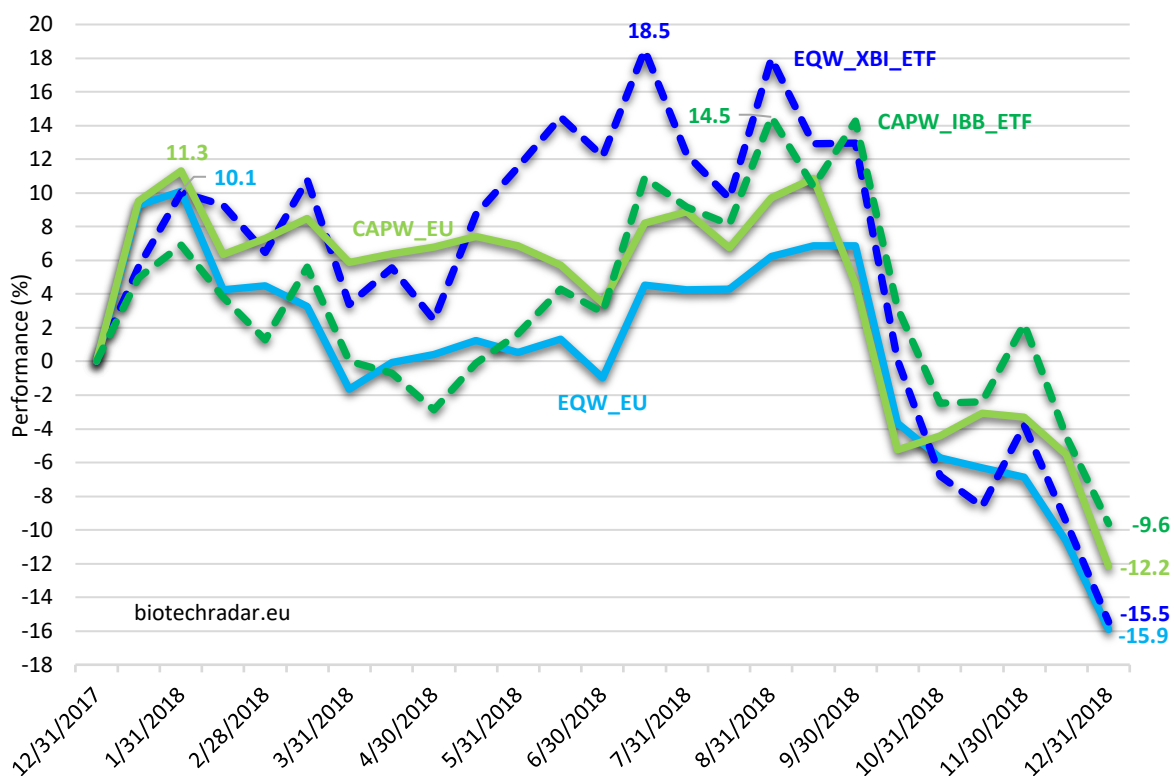


Fig. 26. 2018 performance (%) of 4 indices: European biotech EQW_EU (equal-weighted) vs US biotech ETF “XBI” (equal-weighted), and Europe biotech CAPW_EU (cap-weighted) vs US biotech ETF “IBB” (cap-weighted)

The sector boost in January was also noticeable for the US ETFs, thanks to the “JP Morgan Conference” and overall well-oriented markets. Investors were anticipating a wave of M&As, which was materialized e.g. by the Celgene/Juno and the Sanofi/Bioverativ deals. A large sell-off took place on the markets in February, which according to the indices, even if global, mostly impacted the smaller caps in Europe and the larger caps in the US. Then the “trade war” between the US and China started at the end of March. The US smaller and midcaps managed to outperform the larger caps until the 2-step global market corrections, in October and December (incl. concerns on inflation in the US, Fed rates, trade war intensification, etc...). In this context, the free fall was general. For the US biotech sector, the XBI ETF actually corrected even more than the IBB ETF. For the European biotech sector, the larger caps started to correct slightly before but all the end points converged between -10 and -15%.

Overall, the European performance for larger caps was almost only due to the beginning of the year and neutral until the autumn correction (see also **Figure 27** below). For the European smaller caps, the market correction in February annealed all the early gains. A small rebound was initiated by the Swedish biotech sector during the summer but it could not offer any resistance to the market sentiment reversal later in the second half. The US biotech sector had a very strong second quarter and summer before the free fall.

On **Figure 27**, we represented the stock performances by quartiles of the market cap, determined at the end 2017 (1st quartile=Bottom[0%;25%], 2nd quartile=[25%;50%], 3rd quartile=[50%;75%], 4th quartile=Top[75%;100%]). The outcome is very straightforward: the companies with the largest valuations did better in 2018 (this is not always the case). However, this outperformance is only due

to the 2 months of February and March, the trends being very similar otherwise for the rest of the year. Thanks to the heatmap analysis (not shown), we found that this outperformance over this particular period for top (4th) quartile was driven by 3 factors. The first one is that there were less decliners, in proportion, compared to the other quartiles. The second factor is that the amplitude of the decline was, on average, lower than on the other quartiles. The third factor, to a lesser extent, concerns 1 Belgian company (Mithra), whose stock soared over the period. In terms of distribution at the end of 2018, there were slightly less companies in negative territory in the top quartile versus the rest of the distribution (62% versus 71%, respectively). Moreover, the average performance of both the decliners and gainers was slightly better in the top quartile versus the other 3 quartiles pooled altogether (-44.8% versus -48.3%, respectively for the decliners, and +52.4% versus +48.2% for the gainers). These elements explain the significant outperformance of the largest caps at the end of 2018.

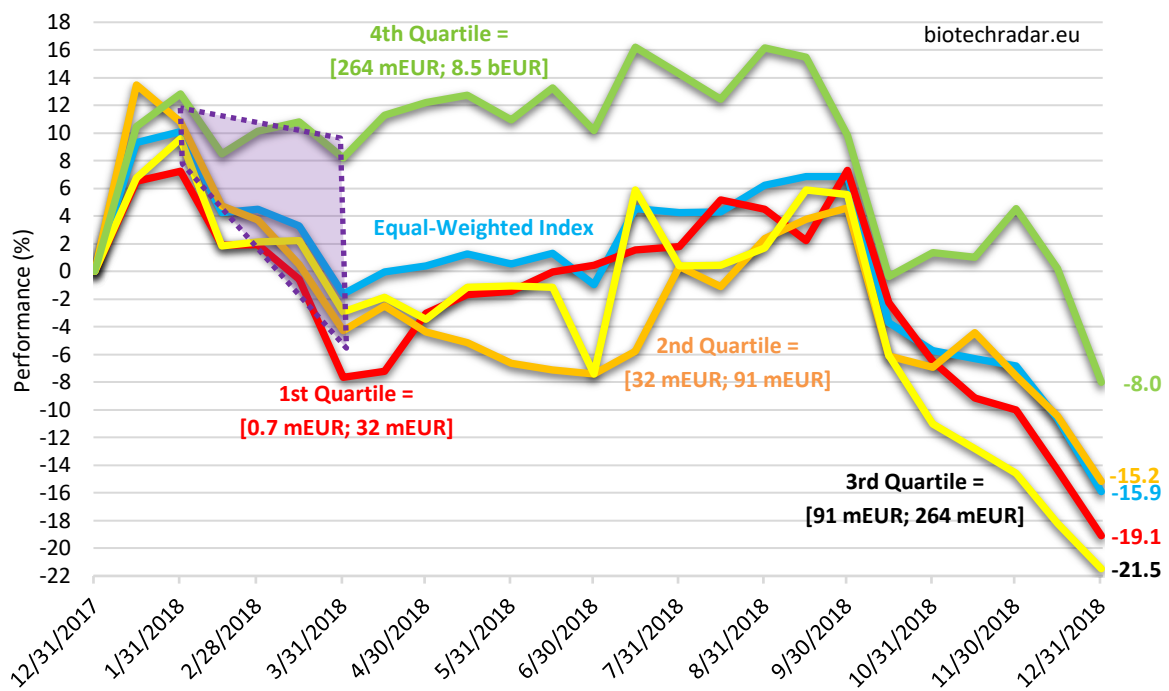


Fig. 27. European biotech index performance (%) in 2018, by market cap quartile as of 31/12/2017 (equal-weighting method)

Finally, excluding macro factors and the early January general sector boost, the correlation between the European and US sector performance was globally weak, which can be explained by the large gaps between the 2 ecosystems. A good example was the number of IPO in 2018, around 50 in the US, the second largest number of the decade (peak in 2014) [16;19-20], while the trend was the exact opposite in Europe (lowest since 2013). On a more positive note, one can also notice that despite challenging market conditions, the European biotech sector did not particularly underperform its US peers. If we compare the relative performance of the main indices, the European indices underperformed the US ones more markedly.

3.3 Market Liquidity

The liquidity on stocks is an important metric for investors, especially for those holding large positions. In this section, we will not focus on individual stocks but on aggregated data for each main stock markets (by operator, not by places). As the level of liquidity varies significantly from company-to-company even within the same market, a finer analysis would be needed to determine what is actually the “most liquid market”. However, we will not provide these data in this introductory report, and we will only report top-level data. The **Figure 28** shows the moving average over 5 sessions (MA5) of the turnovers on each main European stock market. The MA5 was chosen to smoothen the curves, as the daily turnovers can exhibit large variations. Because of the large spread observed for the amounts traded on the various markets, we use a log scale on the y-axis, which has the effect to tighten the excursions of the curve. It also prevents plotting issues of null values on the log scale.

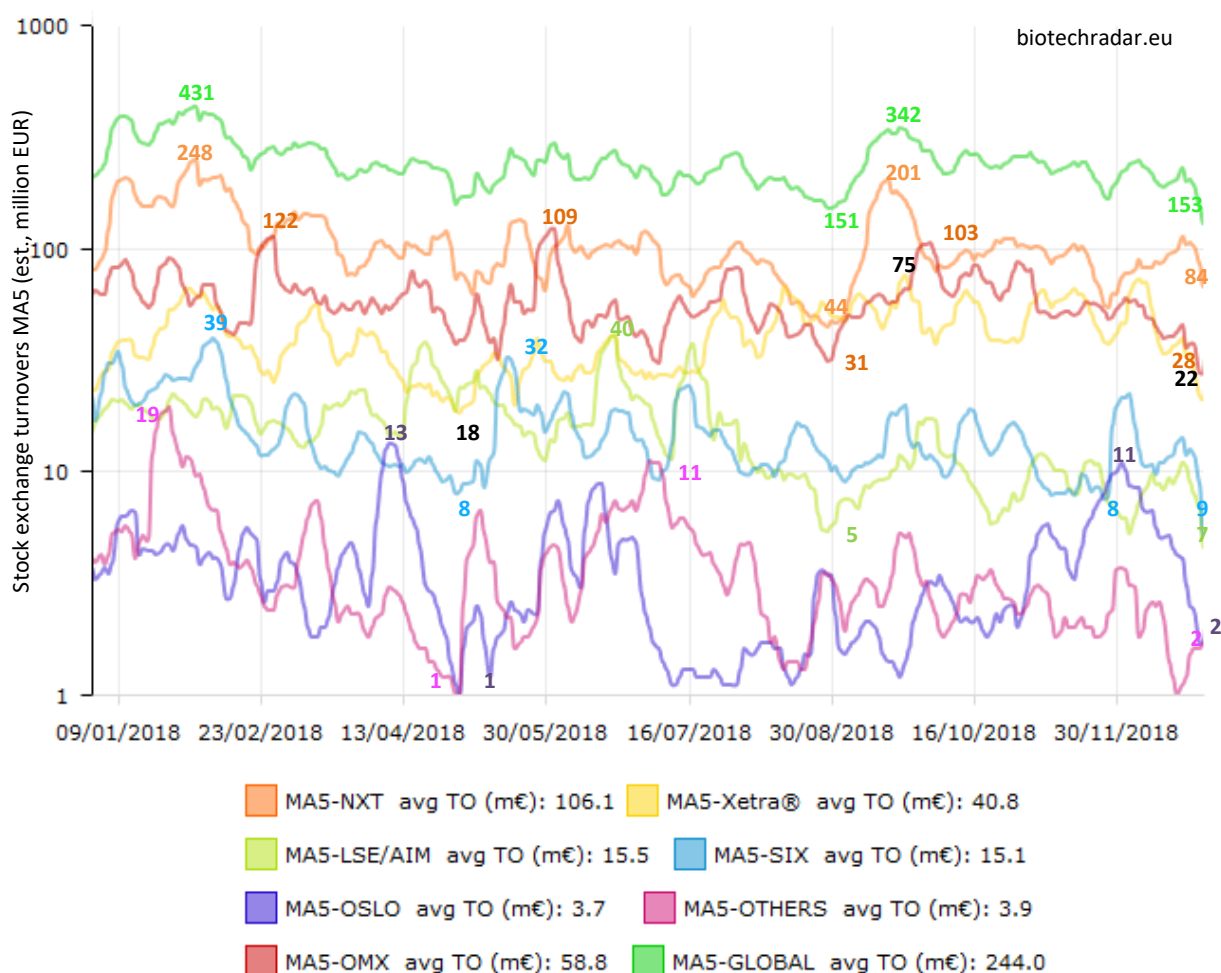


Fig. 28. 5-session Moving Average (MA5) on the turnovers on the European main stock markets during 2018 (daily turnover estimates on an extended universe of 157 European biotech companies and 16 European selected DX companies)

The MA5 basically represents the average turnovers over a week. By using averaged values, a slight delay in the curve responses is induced, but as the time constant is very short, this is a negligible point. The “Others” category includes the turnovers of Borsa Italiana (Milan, Italy) and Bolsa de Madrid (Spain). These turnovers’ data are based on estimates, relying on a formula using as inputs

the classical end-of-day data. These estimates typically provide an accuracy well below 5%, except, potentially, with high levels of intraday volatility (then data are usually corrected with the data reported by the stock market operators themselves).

The universe on which these liquidity data are reported is also slightly extended, with some companies not matching our selection criteria, and 16 selected diagnostic (DX) companies. However, the DX companies do not really induce a lot of distortion, as all the data are highly dominated by the biotech sector. To illustrate this, even if Biocartis (Belgium) had a market cap of 511 mEUR at the end of 2018 (so 3-4% of the total on Euronext), the turnovers on Biocartis stock were only between 0.5 and 2 mEUR, typically, over 2018.

The **aggregated daily turnover at the European level was of 244 mEUR, on average, for 2018** (our universe of select markets). The most active markets were those managed by Euronext (106 mEUR average daily turnover). In fact, this has been the leading place for quite some time now, as they cover both the dynamic Belgium/Netherlands hotspot, along with the large number of companies in France. These data will be complemented by the much more modest 4 mEUR from Oslo Børs from 2019 onwards. The Nasdaq OMX Nordic markets took the second spot with an average of 59 mEUR, thanks to one very large cap (Genmab), and the large number of Swedish companies. The turnovers on Nasdaq OMX spiked occasionally over those on Euronext, but not for long period. The German markets from XETRA are on the third rank (41 mEUR, on average in 2018), mainly thanks to Morphosys and Evotec. During the second half of the year, the turnovers were almost on par with those from Nasdaq OMX. Then, there is a gap again with the LSE/AIM and the SIX Swiss Exchange (averages of 15-16 mEUR each). The very negative trend on LSE/AIM turnovers was clear during the summer, correlating mostly with the plummeting stock of Indivior. The turnovers on SIX included only 10 companies, versus 38 for LSE/AIM (incl. 4 DX), but compared to the total market cap on each market at the end of 2018 (**Figure 29**), both ended under-represented. This was more marked for the SIX markets than the LSE/AIM markets.

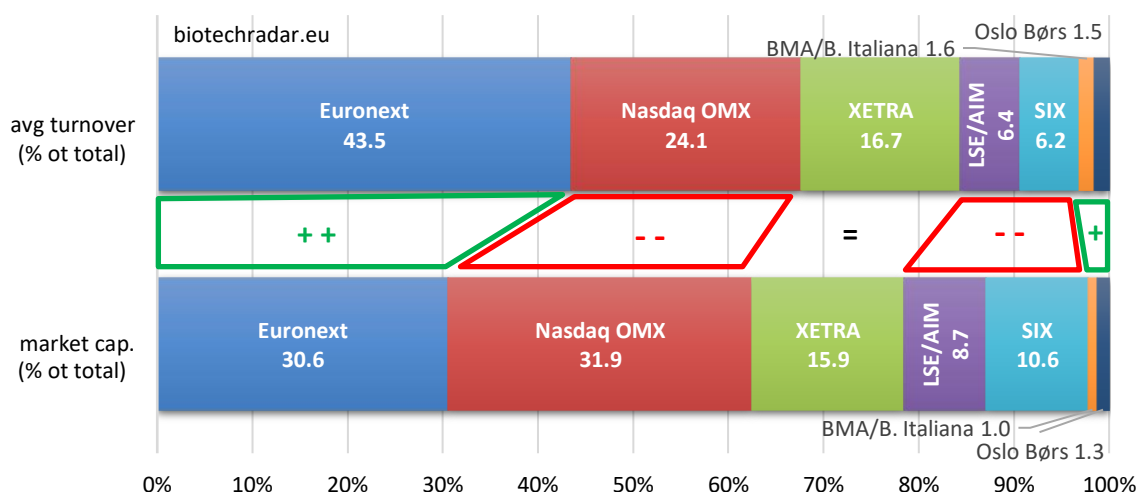


Fig. 29. Comparison of the market cap (extended universe of 173 companies as of 31/12/2018) and turnovers MA5 on the European main stock markets during 2018 (extended universe - see Fig.27)

Overall, from **Figure 29**, the Euronext markets present the most attractive picture in terms of market liquidity. Further metrics support this assertion (not discussed here). The German markets are also

quite strong, all things being relative. **The 3 main European markets in valuation (78.4% of the extended universe) gathered 84.3% of the turnovers.**

This is also illustrated on **Figure 30** below, on the MA20 of the turnovers. Here we used the moving average over 20 sessions to smooth the curves even more, and capture the mid/long-term trends more easily, still by inducing an approximately 1-month delay on curve responses. The domination of the 3 markets previously mentioned is even more obvious here. This representation also allows to capture the market dynamics, like the loss of share of LSE/AIM (UK) during the summer and the rise of the XETRA (DE) over the same period. Following the acquisitions Ablynx (a “large” market cap for a European biotech company), turnovers on Euronext peaked accordingly at the end of January/early February, as observed with a delay on the MA20. Then a global decline of the turnovers followed, over 8 months (seen on **Figure 28**), mainly due to lower turnovers on Euronext. Of note, TiGenix and Ablynx were de-listed in June and July, respectively, explaining partly this decay through the summer. After the summer, and the rebound of turnovers in September, another mid/long-term decline took place, more correlated with deflating turnovers from Nasdaq OMX. This decline also last lasted 8 months into 2019, leading to concerningly low turnovers, actually the lowest over the past 2 years.

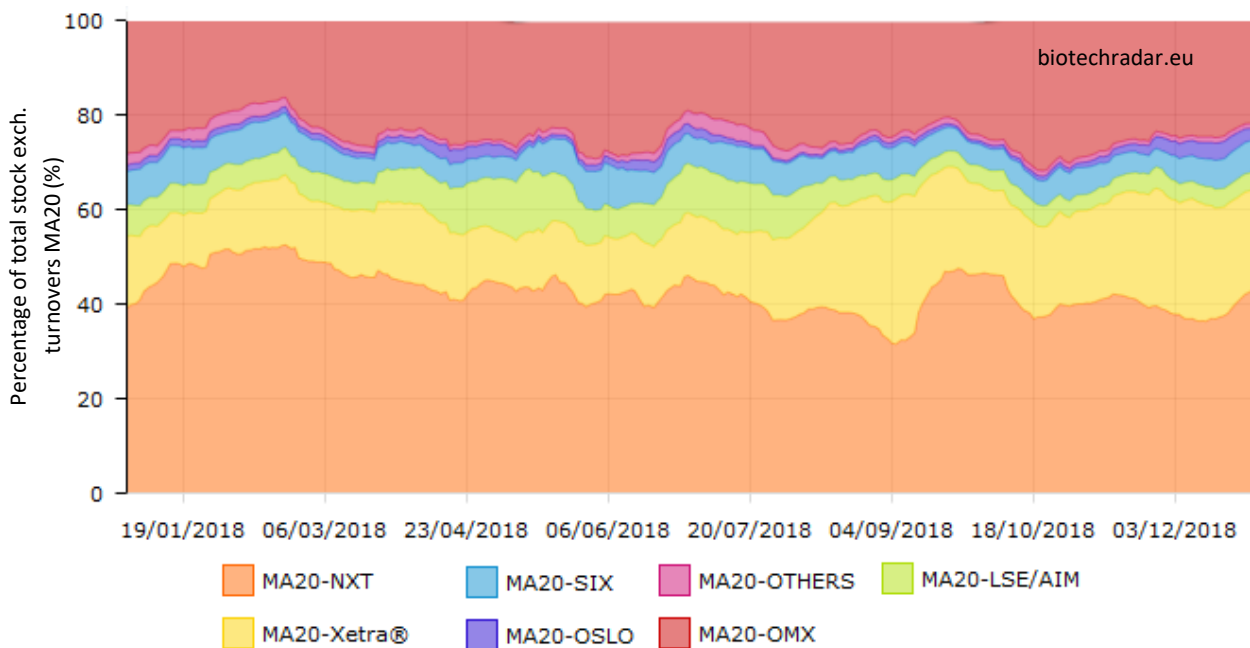


Fig. 30. Repartition of the turnovers MA20 on the European main stock markets during 2018 (extended universe – see Fig.27)

As there is no straight correlation with the evolution of total market cap, it seems that many international institutional investors left the European biotech markets over this period. One may wonder how the emergence of the Hong-Kong markets could have impacted the liquidity in Europe for biotech companies. Indeed, thanks to the new regulations allowing non-profit-generating companies to list on public markets, many biotech/biopharma/pharma companies floated in Hong-Kong in 2018, mainly over the second half. It has to be noticed that 4 out of the top 5 largest 2018 IPOs on the sector took place in Hong-Kong [21]. Even though the profile of these companies is much more late-stage and with broader pipelines than the typical European biotech company, potential arbitrations may have occurred at the expense of Europe, in terms of fund flows.

4. Employment

The 150 companies in our universe counted approximately 15500 employees or FTEs (Full-Time Equivalent employees) at the end of 2018 (or during 2018 for the FTEs). Not all the companies disclose the number of employees at the end of their reporting period, thus the mix. Knowing that this sector drives mainly high-payroll jobs and offers some opportunities for the PhDs, this is an interesting metric to study. This topic could potentially be the subject of further reports.

The number of employees/ FTEs per country, at the end of 2018, is shown on **Figure 31**.

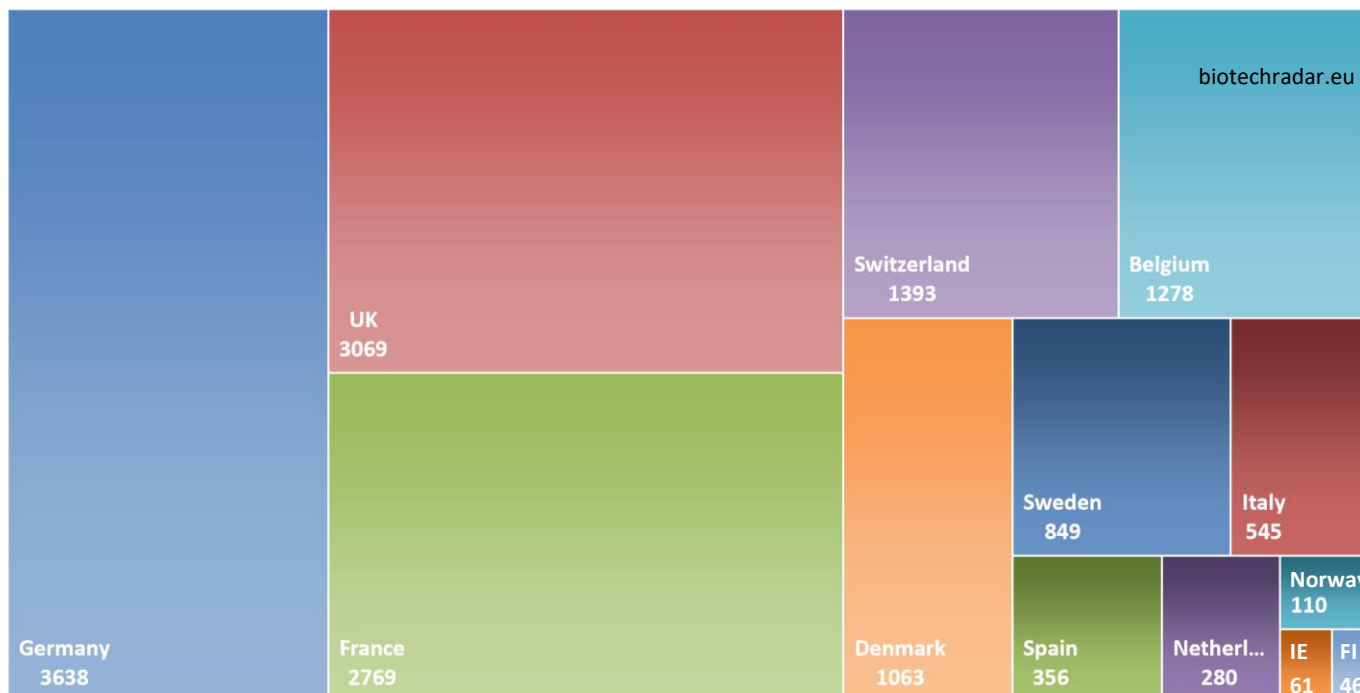


Fig. 31. Number of employees/FTEs for the European public biotech companies, by country (our universe)

The 3 leading countries, by a margin, are Germany, UK and France, representing more than 60% of the total altogether (61%). However, Germany clearly owes this leading position to Evotec, with more than 2600 employees as of 31/12/2018, or 70% of the total of the country. This is explained by the business model of the company, who provide a range of services including drug discovery (segment not covered). That makes the company an outlier for the employment metric, as compared to the rest of our universe (together with the much smaller Oncodesign in France). For the UK, Indivior also gathers circa 30% of the UK total. The British company had already announced that many job cuts would occur in 2019, following the patent cliff for their leading product Suboxone. Given the resilience of the product in the first half of 2019, perhaps these cuts will be smoothed or hopefully decreased or delayed, but the trend is clearly going south. Last on the podium, France numbers are distributed more evenly, unlike Germany of the UK. Switzerland, Belgium and Denmark follow, all with numbers ranging between 1000 & 1500 employees/FTEs. Idorsia and Galapagos account for 54% and 57% of their national total numbers, respectively. Two Danish companies, Bavarian Nordic (419) and Genmab (377) gathered 75% of the employees. Consistently with the profile depicted in this review, Sweden only had 849 employees at the end of last year, because of the “youth” of the companies in general. In addition, many of the Swedish companies in our universe adopted a “virtual

biotech” model (where basically everything is outsourced). Indeed, 46% of them had 10 employees/FTEs or less, which is by far the largest proportion in our universe. Finally, Italy, Spain, the Netherlands, 2 Nordic countries and Ireland included approximately 1300 jobs altogether.

On **Figure 32**, the proportion of employees per country/cluster is compared to the proportion of the number of companies in each country/cluster. The best performers in terms of employment are Germany, Belgium/Netherlands, Switzerland, Denmark, whereas those with the lower impact are the Nordic countries in general.

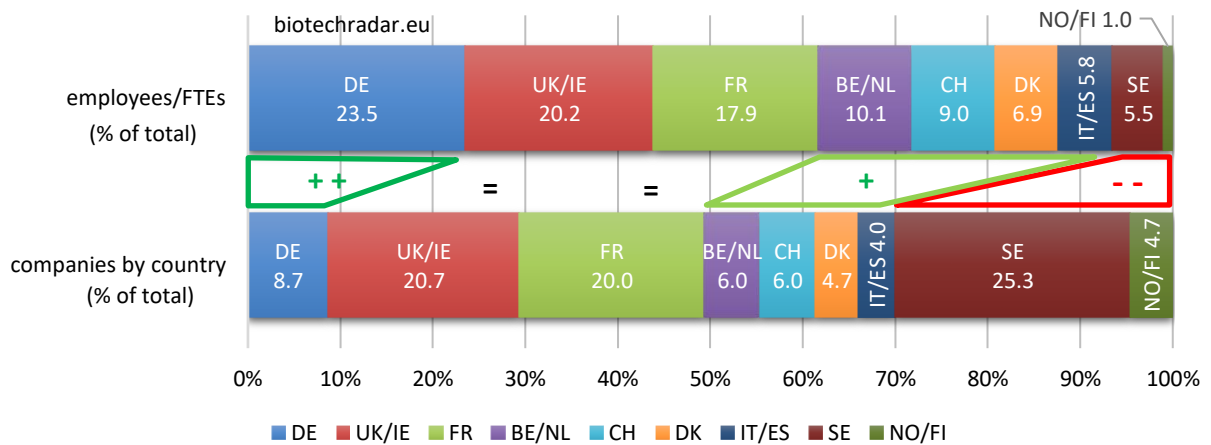


Fig. 32. Distribution of the number of employees/FTEs, by country/cluster

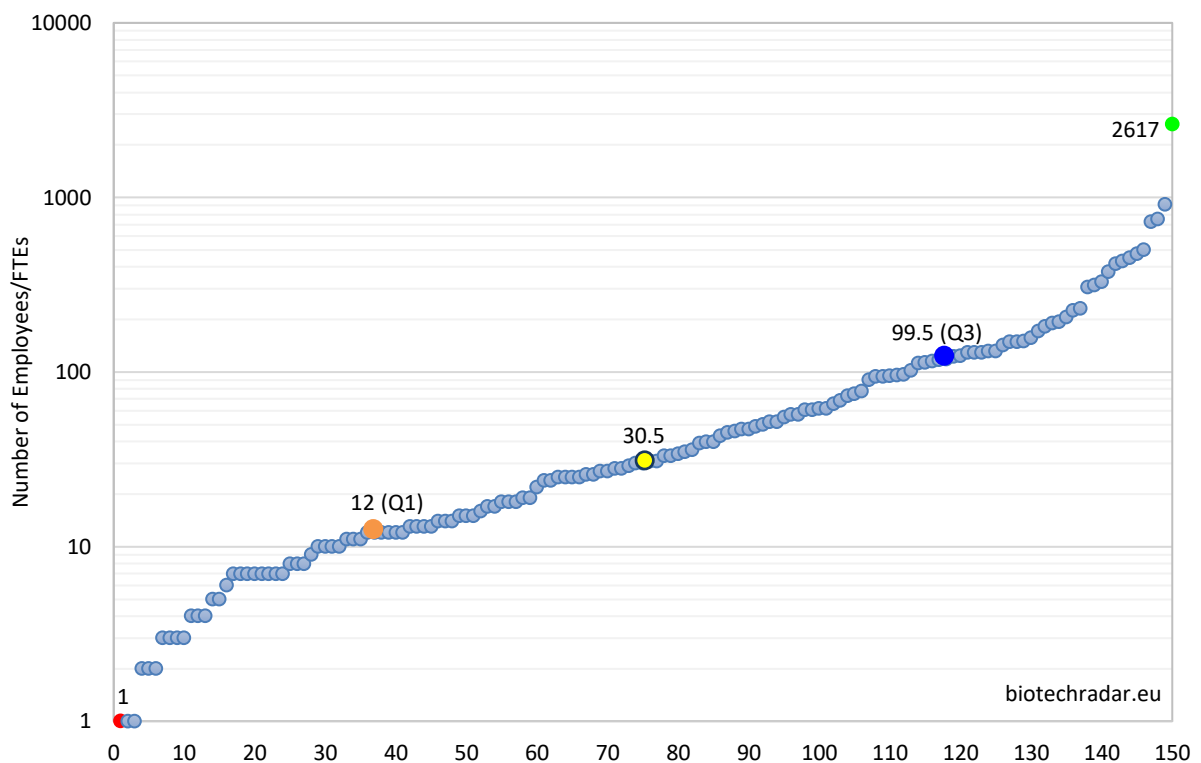


Fig. 33. Employees/FTEs of 150 selected European public biotech companies

Finally, the number of employees/FTEs in each company is shown on **Figure 33**. The readers will observe the striking similarity with the shape on **Figure 19** (market cap of the companies), also with a wide exponential part (attention, these are not the same companies on the x-axis for each chart,

due to the selective sorting for each data series). Without looking at data per company but at a global level, a straightforward model consists in establishing a proportional relationship between the number of employees/FTEs and the market cap on the companies, so that the market cap (in mEUR) is equal to 2.1-fold the number of employees/FTEs (regression on log10 of data series with the method of least squares). However, when comparing this law for each company, we observe a significant spread above and beyond the model curve. We will not go further in this introduction, however there are interesting comments to do from such a modeling.

5. Financing

The 150 European public biotech companies in our selection have raised approximately 3.62 bEUR in 2018, in around 187 operations relating to the financing categories we consider (see Figure 34 for the amounts raised & number of operations by financing category). It has to be compared to approximately 4.25 bEUR in 2017 (-15% year-over-year), with 178 operations in 2017, according to our preliminary numbers (small variations upwards may be expected for 2017).

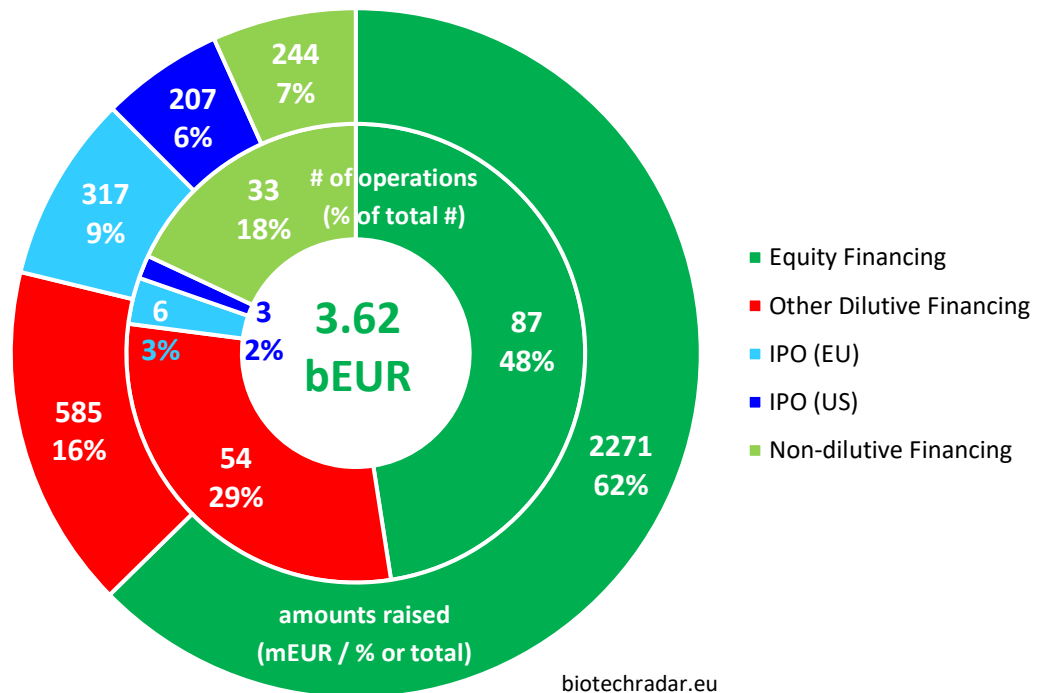


Fig. 34. Amounts raised and number of operations in 2018, by financing category, for the European listed biotech companies in our universe. “Equity Financing” including follow-on/secondary offerings, private placements/directed issues, capital increases with or without preferential/subscription rights; “Other Dilutive Financing” including any kind of equity lines, convertible debt and warrants/options; “Non-Dilutive Financing” including loans, grants (for which the amounts allotted to companies are disclosed), and any kind of non-dilutive debt instrument

Nota Bene: even if some financing schemes are drawn down over time, we count them as fully committed at the signing date in the “amounts raised”, as these figures measure the ability of the companies to find investors or creditors. On the other hand, only actually drawn/booked amounts are considered in the part dedicated to the cash burn figures in section 6.

Overall, **2 thirds of the financing amounts came from “offering”-like financing in 2018, for almost 2.3 bEUR (approximately +37%/+600 mEUR versus 2017)** and 87 operations (stable number compared to 2017), or about **half of the funding operations (48%)**. **The median amount raised in this category was 8.9 mEUR (IQR = [3.7; 22.0] mEUR), as compared to 7.0 mEUR in 2017 (IQR = [2.6; 19.0] mEUR)**. This was a solid performance, offsetting the poor one on the IPO side. As per the 2019 BIO Industry Report [16], **17.5 bUSD (or approximately 14.8 bEUR) were raised in the US from “Follow-On Public Offerings” for “Emerging Therapeutic Companies” in 2018, which is approximately 6.5-fold more than for our European universe.**

Moving to the IPOs, 2018 was much weaker than previous ones in Europe, as we already mentioned. The US IPOs usually allow some European biotech companies already listed in Europe to raise cash amounts in ranges that are not possible in their home markets. However, in 2018, only Morphosys (Germany) managed to raise a significant amount, that was 193 mEUR (239 mUSD).

Biofrontera (Germany) and Tiziana (UK) also managed to dual-list on Nasdaq during 2018, but with much smaller operations (10 and 4 mEUR raised, respectively, amounts that are common in Europe). Overall, the **decline in amounts from US IPOs (dual listings) was 72% (-460 mEUR)**. European IPOs only led to 317 mEUR of cash injections. Here again, the **decline in amounts from European IPOs (our universe) compared to 2017 reached 67% (-640 mEUR)**. Still as per [16], **4.4 bEUR (5.2 bUSD at 1.1815 EUR/USD average FX rate in 2018) were raised in 2018 on the US markets in 49 IPO operations** (including the dual-listings from European companies), so a **tremendous gap between the 2 continents.**

Dilutive financings regrouping any kind of convertibles, equity lines and exercise of warrants/options and helped raising 585 mEUR, but with more than 50 operations (negligible amounts from the exercise of warrants/options missing). This amount is driven for almost 60% by 2 large Convertible Bonds programs for Idorsia (Switzerland) and Cosmo (Italy). More interestingly, in 2018, 15 operations of Convertible Loans/Bonds and Equity Lines (program amounts <30mEUR) gathered 85.6 mEUR, with an average amount of 5.6 mEUR and a median of 3.4 mEUR (compared to 2017: 10 such operations for a total of 97.6 mEUR, 9.8 mEUR average, 10.0 mEUR median). This partly reflects the increasingly challenging conditions for financing in 2018, at least for some of the smallest caps. More of these small caps (still a minority) made use of these categories of financing, but for smaller amounts. The problem is that most of these equity lines and other convertible schemes have become the main or only sources of funding for many of these small companies, instead of being just add-ons to share issues. As raising equity from institutional shareholders is very difficult or impossible for them, these companies subscribe to financing schemes that actually keep them alive, but most of the time at the expense of a long declining journey for the stock price...

Finally, **one fifth of the financing operations were non-dilutive, but only led to 6% of the financing amounts, or 244 mEUR (down 43% versus 2017**, but this amount was impacted by a 140 mEUR bridge loan to Evotec for the acquisition of Aptuit). We will also mention the contribution of the European Investment Bank (EIB), offering several vehicles to support the growth of the biotech companies, usually to support them on their final steps towards commercialization. In 2018, the **loan agreements signed between the EIB and the European listed biotech companies, and the grants awarded (mainly in the frame of the Horizon 2020 program) reached 132.3 mEUR with 6**

operations, a net progress from 2017 (77.4 mEUR but only 2 operations, and including a loan for Evotec of 75 mEUR).

The most important financing operations of 2018 per category can be found on **Table 9**. They represent almost 60% of all the amounts raised/committed last year.

Date	Company	Amount (mEUR)	Comment
Equity Financing			
Q3'18	Galapagos (BE)	297.0	US Offering
Q3'18	Idorsia (CH)	262.5	EU Offering
Q3'18	argenx (BE)	255.8	Combined EU & US Offering
Q2'18	Cellectis (FR)	142.6	US Offering
Q1'18	DBV Technologies (FR)	140.8	Combined EU & US Offering
Other Dilutive Financing			
Q4'18	Cosmo Pharma (IT)	175.0	Convertible Bonds (Unsecured)
Q3'18	Idorsia (CH)	172.0	Convertible Bonds (Unsecured)
IPO (EU)			
Q2'18	Polyphor (CH)	139.2	IPO on SIX Zurich (CH)
Q3'18	Calliditas Ther. (SE)	71.6	IPO on Nasdaq OMX Stockholm (SE)
Q1'18	Acacia Pharma (UK)	40.0	IPO on Euronext Brussels (BE)
Q4'18	MedinCell (FR)	31.4	IPO on Euronext Paris (FR)
Q4'18	Alzecure Pharma (SE)	19.4	IPO on Nasdaq OMX Stockholm (SE)
Q3'18	Asarina Pharma (SE)	15.6	IPO on Nasdaq OMX Stockholm (SE)
IPO (US)			
Q2'18	Morphosys (DE)	193.1	Nasdaq IPO
Q1'18	Biofrontera (DE)	10.4	Nasdaq IPO
Q4'18	Tiziana Life Sci. (UK)	3.9	Nasdaq IPO
Non-dilutive Financing			
Q3'18	Nanobiotix (FR)	40.0	EIB Loan
Q4'18	Newron Pharma. (IT)	40.0	EIB Loan
Q3'18	Bavarian Nordic (DK)	30.0	EIB Loan
Q3'18	Acacia Pharma (UK)	25.8	Credit Facility
Q1'18	MedinCell (FR)	20.0	EIB Loan
Q2'18	Pharnext (FR)	20.0	Bond Loan

Tab. 9. Most important financing operations in 2018, by amount and category. Given the small number of IPOs both in Europe and in the US, these operations are all listed in this table.

The breakdown of the amounts raised in 2018, by country/cluster and by stock market operator, is shown on **Figure 35**.

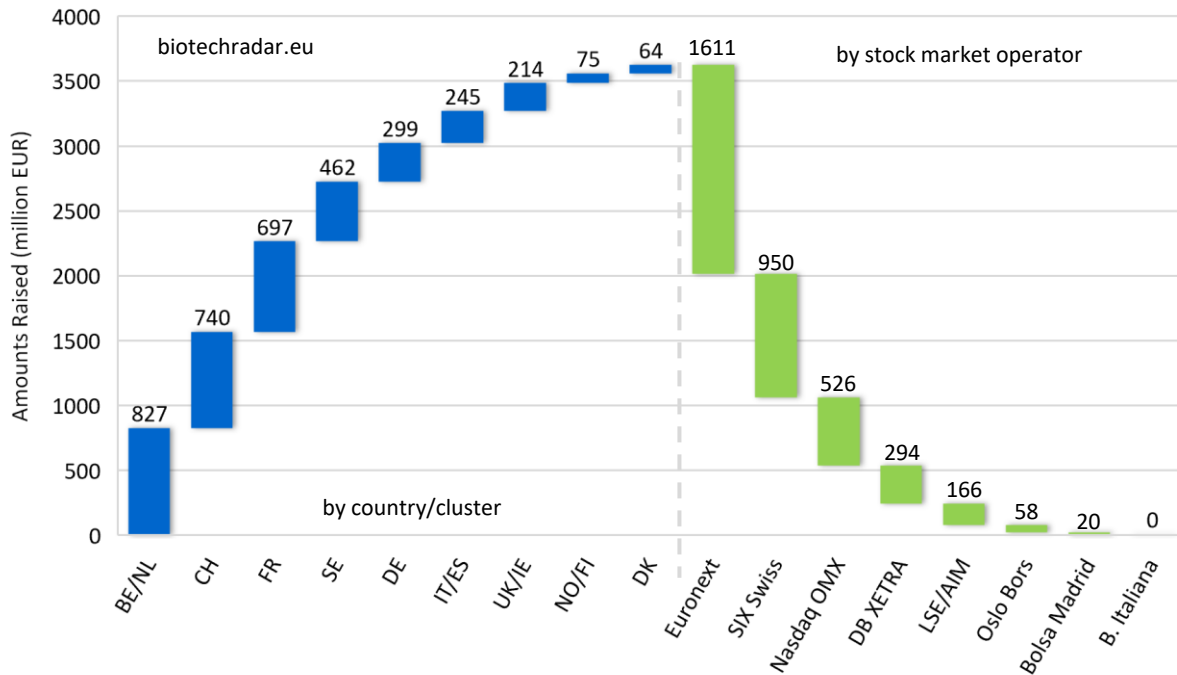


Fig. 35. Amounts raised in 2018, by country/cluster, and by stock market operator

The top 3 countries/clusters (Belgium/Netherlands, Switzerland and France) gathered 62% of the total amounts, with amounts ranging from 697 to 827 mEUR. With a significant drop with respect to France, Sweden managed to raise 462 mEUR. Then the amounts fall again quite significantly for Germany, Italy/Spain, UK/Ireland, all in the 200-300 mEUR range. Finally, the smallest cluster Norway/Finland raised 75 mEUR, while Danish listed biotech companies had only raised 64 mEUR.

To support the interpretation of the “performance” with respect to the amounts raised in each country/cluster, we added the **Figure 36**, which introduces a comparison with a reference. This reference can be viewed as a simple model, reflecting the amounts of financing needed for a pool of “n” companies, only using a given percentile of the distribution of the market cap and a fit -constant-parameter (see **Annex 1** for explanations).

When compared to the simple model estimates (60th-percentile market cap, times number of companies, divided by a constant ratio) on **Figure 36**, the main deviation arises from Denmark, which can be explained by the small number of companies and the fact that they were almost all funded well over the end of 2018, except Oncology Venture, a small cap biotech (European referential!). On the other side, Switzerland raised more money than the model estimate. This can be mainly explained by Idorsia, who managed to raise more than 430 mEUR in 2018. Polyphor’s successful IPO in Zurich also generated an inflow of almost 140 mEUR for the company. Germany is also slightly short compared to the model estimate.

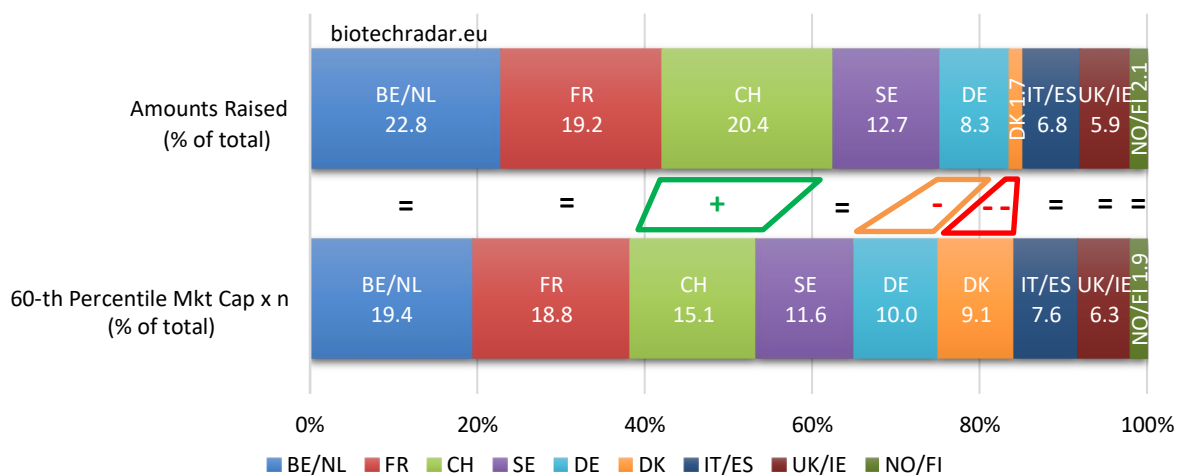


Fig. 36. Amounts raised in 2018 compared with a simple model reference (60th-percentile market cap x number of companies / constant ratio), by country/cluster – see model explanation in the text

6. Other financial metrics: cash burn, extra cash sources, cash balance, profits & losses

This section complements the previous part dedicated to inflows, first by comparing with the outflows (cash burns), and then by diving into the inflows again with the non-negligible contributions from extra (non-recurring) sources of cash, mainly from partners. We will finally have a look at the cash balance between all these contributions, consolidated at country/cluster level.

6.1 Cash burn

The amounts of cash burnt during the 2018 financial period are shown on **Figure 37**, by country/cluster. Before commenting this figure, we need to make a few comments and introduce our methodology. One problem is that not all the companies report their financials with an alignment of the financial reporting period with the calendar year. Around 10% of the companies report their financials with shifted periods, sometimes not even aligned with a quarter! Moreover, the reporting rules in Europe (quarterly or half-year reports) are different from the US, also being different from one country to another (some reports are only done every 6 months). This is why we will consider that the so-called “2018 financial period” data thereafter matches with the reporting periods including the larger number of months into the 2018 calendar year. For the companies reporting from 01/07 (July 1st) to 30/06 (June 30th), the “2018 period” will be the data from 01/07/2017 to 30/06/2018.

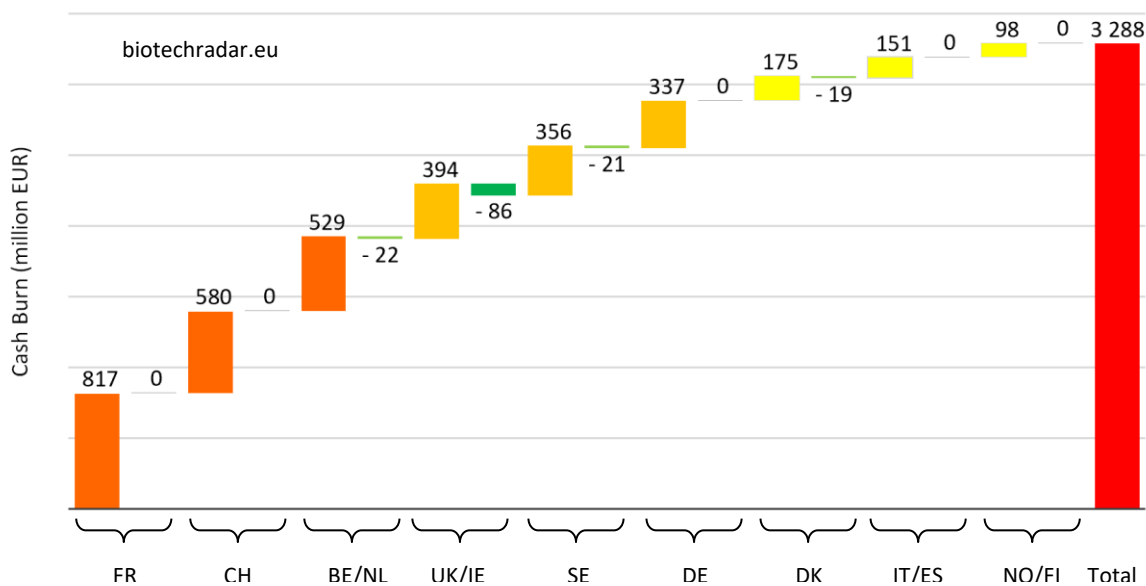


Fig. 37. Cash burn (mEUR) for the 2018 reporting period, by country (our universe): positive and negative contributions (outflows and inflows, respectively)

We define the cash burn by taking into account the following contributions:

- we compute the difference in cash and cash equivalents (or variants used by companies, usually including current/short-term financial instruments) from one full-year reporting period to the next (data actually available by quarter/half-year on biotechradar.eu)
- we add up the inflow contributions from financing activities (those actually taken into account for the cash and cash equivalents, not those from P&L)
- we also add up the contributions from non-recurring revenues, or “extra sources” of cash, namely cash upfront & milestone payments from partners, revenues from legal activities (e.g. awards from litigations), and business/asset divestments (e.g. subsidiaries, real estate, stakes in other companies)
- we do not add up the contributions from recurring revenues, and even if they may vary from one reporting period to the next. Are thus excluded the royalty streams, or the incomes from national R&D tax credit schemes (since we are talking about companies with high R&D expenditures, these credits are by definition recurring)
- the non-recurring expenses are excluded, since the global underlying idea is to establish “worst-case” estimates for this metric (to infer the cash runways, also available on biotechradar.eu)

Note that some companies report their “net” cash burn, while others report their “operating” cash burn. In fact, there is no standard method. As indicated by the amounts for the negative cash burn contributions (inflows) from **Figure 37**, only a few companies have a negative cash burn, as per our method. This usually correlates with a positive net cash flow generation. Once again, the cash burn numbers are consistent with the profile of the companies in our selection, with high R&D expenditures. Lastly, depending on companies’ accounting methods, our cash burn calculations may or may not fit with the operating expenses of the companies (see **Annex 2** for a comparison).

Overall, **the total cash burn reached 3.29 bEUR for the 150 European biotech companies in our selection in during their 2018 reporting period, including 3.44 bEUR of positive cash burn (cash outflows) and 150 mEUR of negative cash burn (cash inflows)**. The Top 3 countries found on **Figure 35** (cash raised) are also the top 3 spenders -in a reverse order- with more than 500 mEUR burnt. Only ranked 7th on the cash raised, UK/Ireland is ranked 4th when it comes to the cash burn. The rest of the ranking is also almost the same as on **Figure 35**, except that Denmark is up by 2, in agreement with the overall comfortable cash positions of these companies. So basically, **Figures 35 and 37** are very consistent. What remains positive, as a whole, is that even if 2018 was a tough year for the European public biotech companies, the amounts raised or committed during the (calendar) year were in the range of what was burnt over the 2018 reporting period. One can also see it the other way: companies globally adjusted their operating expenditures based on their cash runways.

Without statistics at company level, the interpretability of the comparison of **Figures 35 and 37** remains limited, because of the variability from one company to another. We will partly answer to this question of interpretability with these numbers: **approximately one third of the companies (35%) had less than 12 months of cash runway, and two thirds (65%) had more than 12 months**. These numbers were calculated retrospectively by comparing the cash and cash equivalents at the beginning of the 2018 period and the cash burn at the end of the 2018 period. **One third of the companies in our universe had more than 24mo of cash runway**, assuming the cash burn from one year to another is constant, which actually is a best-case scenario. Indeed, it usually increases year-over-year for the correctly-funded companies. Hence, an adjustment would be required, but for simplicity's sake, we will keep this number as is. In conclusion, we can say that between 35 and 50% of the companies had to manage their cash very carefully during the last reporting period, while around 25-30% had much more flexibility.

6.2 Extra sources of cash

These include the extra sources of cash, outside those from financing activities (see **Figure 35**). Indeed, there are 3 main sources of additional financing we will consider in this section:

1. Cash considerations from upfront or milestone payment from collaborations or agreements with partners
2. Revenues from legal activities (mainly awards from Court decisions from various litigations)
3. Divestments of assets (e.g. real estate, stakes in other companies)

The **Figure 38** recapitulates the amounts originating from all these categories in 2018. **The grand total at the European level, adding both the financing activities and the extra sources of cash, reaches 4.6 bEUR in 2018 (3.62 bEUR from financing activities, and 0.97 bEUR from extra sources)**.

Overall, more than 970 mEUR were collected from these additional sources during the 2018 reporting periods. In fact, these funds originate almost exclusively from partners, as there were only few awards from legal activities and only few divestments as well, over the period. For these reasons, we can estimate that around 90% of these 971 mEUR came from partners. Of note, only 39 companies (26%), mostly with a late-stage profile, reported non-null extra cash amounts, as one could expect. These amounts reflect how the companies manage to create value with their assets at a point in time.

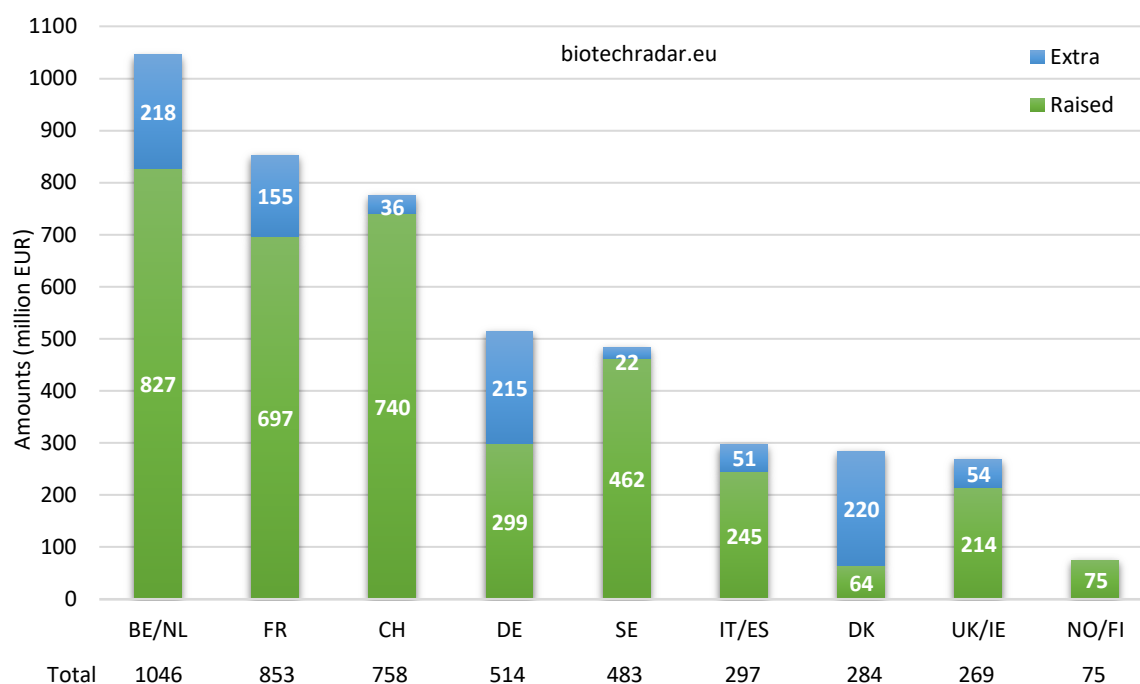


Fig. 38. Amounts “raised” from financing activities and amounts originating from “extra” sources of cash (partners, legal, divestments) in 2018, by country/cluster – grand total of 4.6 bEUR

There were 4 countries/clusters leading by a margin. Denmark’s short lead over Belgium/Netherlands and Germany can be attributed to Zealand Pharma (sale of Soliqua/Suliqua and Lyxumia/Adlyxin for 205 mUSD). Galagagos (126 mEUR) and Mithra (69 mEUR) drove the numbers up for Belgium/Netherlands, while Evotec (multiple partnerships generating almost 150 mEUR of disclosed upfront and milestone payments) and Morphosys (almost 50 mEUR) contributed the most for Germany. Consistently with previous comments about France, the additional cash came from a more “uniform” distribution, and was not dominated by only 1 company in particular (9 contributing companies including Innate Pharma, Adocia and Poxel for 2 thirds of the 155 mEUR). With much smaller amounts, around 50 mEUR, UK/Ireland and the Southern Europe cluster rank 5th and 6th. Switzerland and Sweden gathered even lower extra amounts, from 20 to 36 mEUR each, while Norway/Finland collected simply no extra (small number of early/mid-stage companies).

Finally, we can see that the extra amounts represented a significant proportion of the total cash (financing and extra) only for 2 countries: Denmark (77%), due to a non-recurring revenue from an exceptional transaction, and Germany (42%), more due to the business model of the 2 R&D powerhouses that are Evotec and Morphosys, and therefore less likely to vary over time.

6.3 Balance between cash raised and burnt

In this section, 2 balances will be calculated: a first one that we will call “intrinsic”, representing the difference between the amounts raised/committed and the cash burnt during 2018 without accounting the extra cash, and a second one including the extra cash, so including “extrinsic” or non-recurring elements (even though partnering is definitely part of the business model).

The first balance “Raised - Burnt” (raised minus burnt) is represented on **Figure 39**, along with the “Burnt/Raised” ratio.

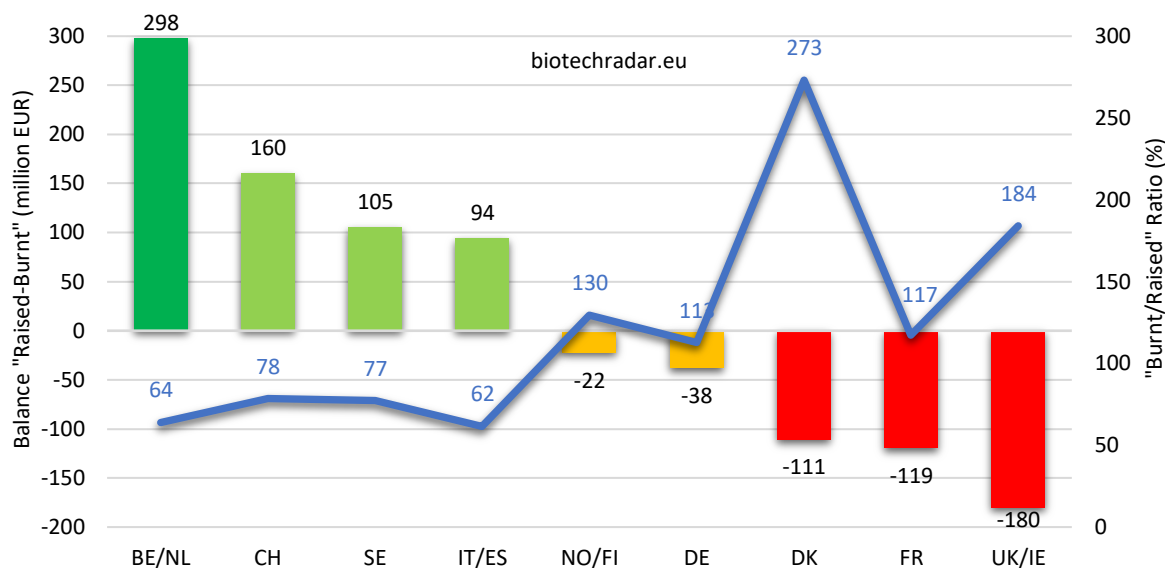


Fig. 39. Cash balance “Raised - Burnt” & “Burnt/Raised” ratio for 2018, by country

For this first balance category, 4 countries/clusters have a positive balance and 5 display a deficit. Belgium/Netherlands leads with a gap of 120 mEUR on the second place, thanks to a good health on the financing side (ranked 1st) but only the 3rd place when it comes to the cash burnt. Ranked 2nd for both the cash raised and burnt, Switzerland still ranks 2nd here. Sweden and Italy/Spain follow, with a positive balance of around 100 mEUR. Of note, Sweden has the best balance of the 3 main countries/clusters, with France and UK/Ireland lagging and even worse, ending on the bottom 2 of this ranking, both with negative balances over 100 mEUR. As highlighted before, the financing environment proved to be challenging in these countries. On the contrary, this is more a glitch for Denmark. Norway/Finland and Germany are almost neutral. **The healthiest sectors had “Burnt/Raised” ratios between 60 and 80%, while those close to neutral but negative had ratios between 110 and 130%.** Of note, from a ratio standpoint, France can be rated as neutral, despite an antepenultimate rank. UK/Ireland’s ratio (180%) looks bad, highlighting an unsustainable situation. These numbers can also to be compared with the number of companies or the market cap per country, but we will remain “high level” here.

The ranking for the second balance, including the extra cash contributions (also added on ratio denominator), is shown on **Figure 40**. As it takes all the contributions into account, the picture is de facto more global. Only the UK/Ireland cluster exhibits a deficit, which clearly reflects the down sentiment over the British sector in 2018. The numerous clinical failures that were announced last year did not help. For France, another main contributor for the number of companies, the extra contributions managed to offset the deficit shown on **Figure 39**, allowing the sector to end just neutral, like Norway/Finland. Belgium/Netherlands confirms its supremacy in Europe, at least on these figures, with a net positive balance exceeding 500 mEUR. All inclusive, the rest of the field demonstrates a relatively healthy situation, with positive net balances ranging from 100 to 200 mEUR. This normalization is also confirmed by ratios well below 100% for 2 thirds of the field. France’s neutral balance indicates that this metric should be under scrutiny for the next few years to

come. For Norway/Finland, the small number of companies may induce more variability on this metric. UK/Ireland’s issues are once again confirmed on this chart.

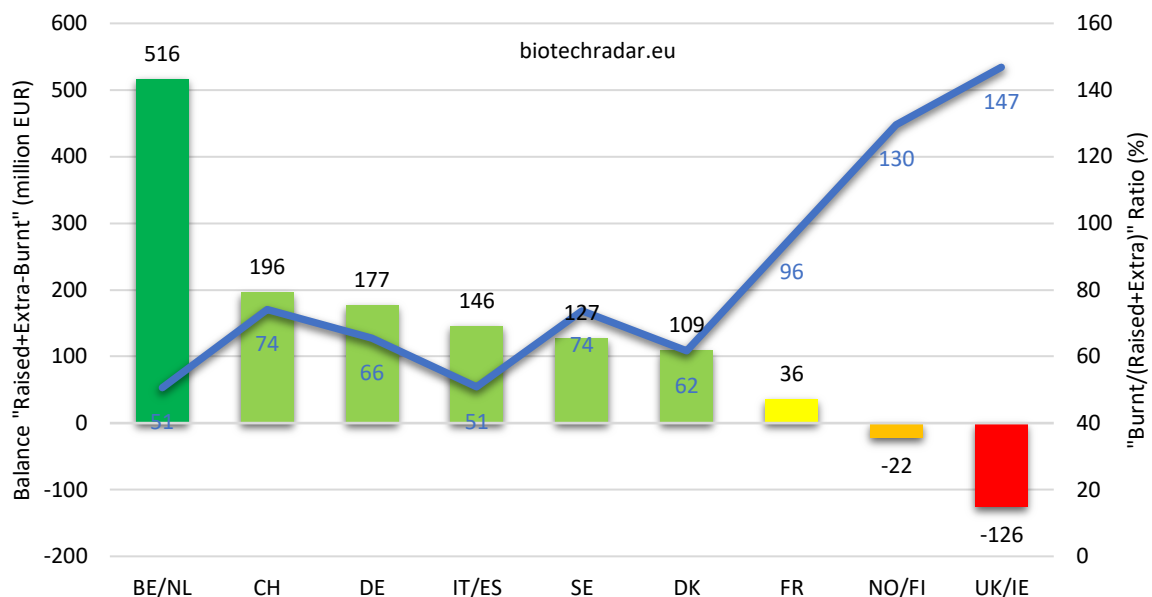


Fig. 40. Cash balance “Raised + Extra - Burnt” & “Burnt/(Raised + Extra)” ratio for 2018, by country

In conclusion, these metrics may not be very sensitive, but they at least provide qualitative and quantitative numbers on how virtuous (Belgium/Netherlands) or difficult (UK/Ireland) a cycle can be, on the key items that are financing and cash management. Healthy, not so healthy and unsustainable situations have been spotted. One also has to keep in mind that the same way the book-to-bill indicator provides a prospective view on sales dynamics, the “Burnt/Raised” or “Burnt/(Raised+Extra)” ratios provide prospective views on how cash runways are to evolve in the near future. Finally, given that R&D expenditures are typically expected to increase on a year-over-year basis (despite an offset by the attrition on R&D programs), neutral global balances and even more negative ones, like those reported on **Figure 40**, provide indications on the global likeliness of negative impacts on companies’ ability to deliver in terms of product development. Operationally, low levels of financing will be translated into shifts in the timeline of certain R&D programs, or even discontinuations due to arbitrations in worse cases (the worst-case scenario being the bankruptcy, 1 case in our selection in 2019 with FIT Biotech in Finland).

6.4 Profits & Losses

The financial data by country/cluster from the condensed income statements can be found in **Table 10**. Whereas there is no real point to interpret such data by country as is, these data can still be compared with the cash balance data from the previous section. Other indicators, like the median gross margin for the companies eligible to report one, as well as the percentage of operating expenses dedicated to Research and Development, are also reported in this table.

Overall, the ranking is very close to the one from **Figure 37**, which is consistent. However, the direct relation between our method to calculate the cash burn and the data out from the income

statements has to be established (see **Annex 2** for a “tentative” data reconciliation). For the 2018 reporting period, 88% of the companies had a negative operating result, and 89% a negative net result, with a quasi-perfect concordance for the sign of both metrics (99.3%).

	EU	FR	CH	BE/NL	SE	UK/IE	NO/FI	DE	IT/ES	DK
Sales of Products/Services	2469	128	119	142	84	1261	0	433	236	67
Other Op. Income	1866	420	106	419	104	34	2	187	28	566
COGs, Cost of Services/Sales	-737	-61	-22	-27	-19	-230	0	-274	-70	-34
Operating Costs	-5449	-1109	-741	-736	-399	-1238	-102	-430	-269	-425
Operating result	-1850	-623	-538	-201	-230	-174	-100	-84	-74	174
Financial Exp. & Taxes	38	12	-31	-32	4	43	2	18	13	9
Net result	-1812	-611	-569	-233	-225	-131	-98	-66	-61	183
n=	150	30	9	9	38	31	7	13	6	7
median Gross Margin *	74.6%	71.2%	83.0%	60.3%	78.1%	65.9%	N/A	88.3%	70.2%	49.0%
* N=	33	3	2	2	5	9	0	7	4	1
R&D Exp./Total OpEx	74.0%	76.6%	77.0%	75.3%	74.6%	63.6%	75.6%	68.0%	51.8%	84.8%

Tab. 10. Condensed P&L and indicators, by country/cluster, for the 2018 reporting period (million EUR)

In terms of gross margins, the medians per country/cluster range from 60% to 90%. These variations may be mainly deemed to the ratio of companies receiving royalties at basically 100% gross margin, with respect to those selling products directly, with an inherent lower gross margin. This large variability is also impacted by the low number of companies in some countries/clusters. Finally, the gross margin data rely on the financial reports of 33 companies out of the 150, which is consistent with the 21% of biotech companies at the commercial-stage (**Figure 6**).

For the ratio of the total operating costs dedicated to R&D, we had to mix financial data already compliant with the IFRS accounting standard, with other various accounting methods. Some non-IFRS data still do include R&D expenses, while some others do not. In this case, we built an equivalent indicator with available data, consistent with IFRS methods or not, basically by taking the total operating expenses and removing the SG&A expenditures. Depreciations are also removed from the calculations of the ratio. We find a **median of 75% of the total operating expenses allocated to R&D**, based on the reports of all the companies. Once again, this validates our company selection. Lower ratios tend to indicate more mature companies transitioning to a biopharma model, with more expenditure allocation to SG&A and commercial activities.

7. Deals

In this section, we will review the deal flow of 2018 for the companies in our universe, and make a particular focus on the out-licensing deals (excluding the in-licensing activity). As represented on **Figure 41**, we grouped the **119 deals signed in 2018, coming from 54 companies (36% of the total)**, in 6 main categories: the out-licensing deals (of products/platforms), the IP (out-)licensing deals, the R&D collaborations, the supply/distribution deals, the sales/divestments of assets (products, subsidiaries) and the Joint-Venture deals (deal model in terms of economics in italic).

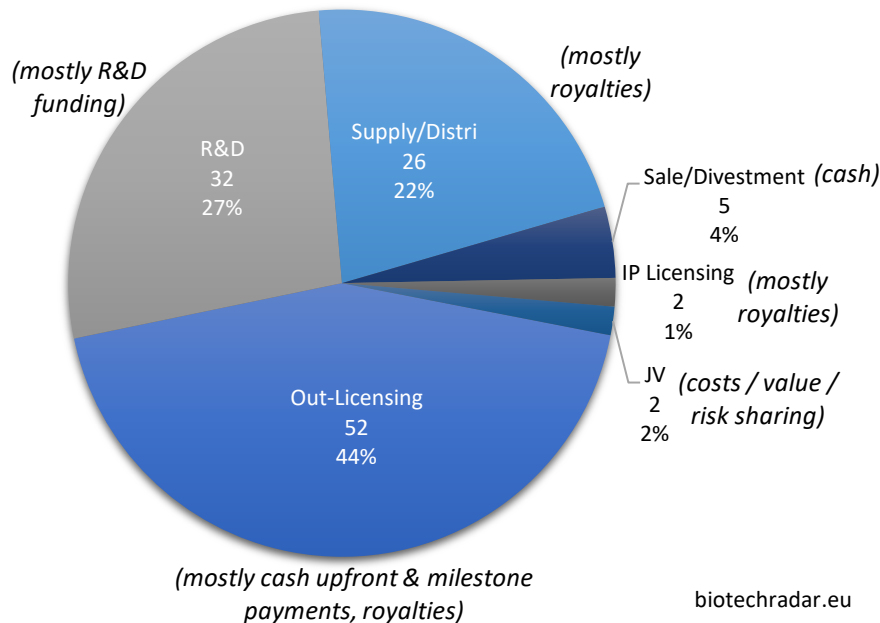


Fig. 41. Distribution of the 2018 deals by category (number of deals / proportions %) from 54 listed European biotech companies, out of the 150 in our universe

The **52 out-licensing of products in development, at various preclinical and clinical stages**, represented 44% of all the 119 deals in 2018, complemented by 22% of supply/distribution deals, usually of commercial-stage products (these deals also normally include the licensing rights for the agreed territories). The remaining third is mainly composed of R&D collaborations (27%), with usually limited cash inflows in play, and sometimes small cash outflows as well.

The direct cash injections mainly came from the upfront part of the out-licensing deals, as well as sales and divestments. Overall, **the total value of all the deals signed in 2018 reached more than 13.4 bEUR, including 13.1 bEUR from out-licensing deals alone. The European sector collected 1.16 bEUR of cash (all deal categories included), of which 886 mEUR from out-licensing deals only.** Of note, these data only rely on the disclosed figures. For many deals, “the financial terms were not disclosed”, as it is usually mentioned in the press releases. For others, only partial data are available, typically when the split is not provided for the upfront and the milestone payments.

The fact that the total cash upfront amounts during 2018 -all deal categories included- differ from the numbers provided in **section 6.2** is explained once again by the misalignment between the instantaneous recognition of the deal considerations in this section, and the actual recognition of these considerations (deferred payables from a “cash position” standpoint). For 2018, the booking of 2 large upfront payments was deferred into early 2019 (calendar year), for more than 300 mEUR: it came from 2 deals inked towards the end of the year, the argenx/Janssen and BioArctic/AbbVie deals from **Table 11**.

The number of deals per country/cluster (out-licensing & all-category/x-y part) are shown on **Figure 42**, along with the number of unique companies who out-licensed in 2018 for each country (dot size).

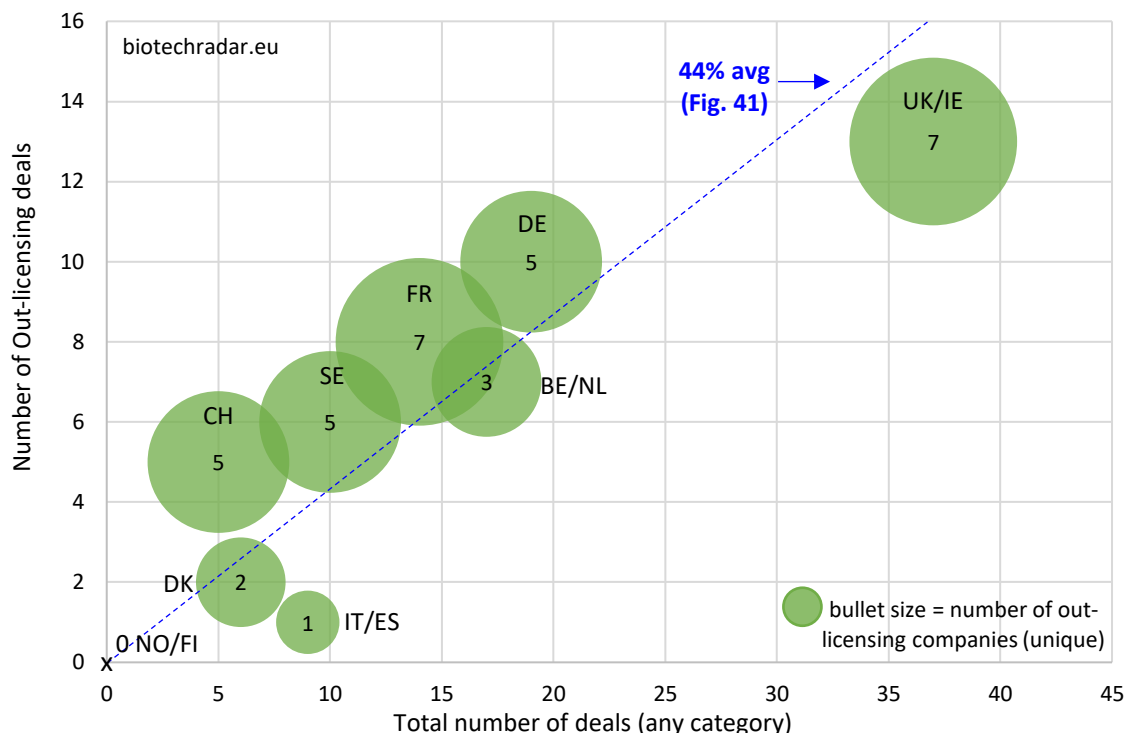


Fig. 42. Proportion of out-licensing deals for each European country/cluster in 2018, out of the total number of deals (all category included)

While the UK/Ireland particularly perform for the number of deals, the number of British companies who out-licensed is not really important in proportion to the deal activity. Indeed, the activity on out-licensing deals was driven by 2 “platform” companies (7 in total), Avacta and Oxford Biomedica (6 out of 13 total deals). For France, the same number of companies (7) generated less out-licensing deals (8, out of 14 total deals or 57%). Of note, the total number of deals for the UK/Ireland was favorably impacted by 8 distribution deals for Lojuxta from Amryt (Ireland), and 13 R&D collaborations. Sweden, another large contributor in number of companies, did not generate many out-licensing deals (6 out of 10 total deals), in line with the lower number of late-stage assets in this country, as compared to France and UK. In Germany, the deal activity was clearly dominated by Evotec, with 12 out of 19 total deals involving the German company. Of these 12 deals for Evotec, 5 were out-licensing deals and 7 R&D collaborations, which fits once again with the business model of the company. Nevertheless, 4 other German companies managed to sign an out-licensing deal (including 2 for Morphosys). Switzerland generated 5 out-licensing deals, including 2 deals between Swiss companies in our universe (Idorsia to Santhera for an option concerning the DMD drug vamorolone, and Polyphor to Santhera for POL6014). For Belgium/Netherlands, the out-licensing deal activity (7 out of 17 total deals) only came from Mithra, argenx and Galapagos. However, the sizes of the deals, and particularly of the cash upfront payments, were particularly interesting (4 out of the Top 10 deals by cash upfront amount, see **Table 11** below).

Based on data partially of fully disclosed by the companies, the **Tables 11 and 12** list the Top 10 out-licensing deals in 2018, by cash upfront and total amounts. The main deal characteristics are also included (more deal details available via the service on biotechradar.eu).

Product(s)	Indication(s)	Out-licensing Company	Clinical Stage	In-licensing company	Territories	Cash Upfront (mEUR)	Max Total (mEUR)
ARGX-110; cusatuzumab	AML; MDS	arGEN-X (BE)	phase 1/2	Janssen / Johnson & Johnson (US)	WW, co-promotion option for US	264.2	1585.2
IPH52; IPH4301: IPH-Siglec-9; 2 Other PC targets	Solid Tumors; Lymphoma; Melanoma	Innate Pharma (FR)	pre-clinical	AstraZeneca / MedImmune (UK)	WW, co-promotion option for EU	61.0	3832.8
EVT-CELG-ONCO	Solid Tumors	Evotec (DE)	research	Celgene (US)	WW	55.1	55.1+
MOR106	Atopic Dermatitis	Galapagos (BE) / Morphosys (DE)	phase 2	Novartis (CH)	WW	47.5 each	472.5 each
MP0310	Cancer	Molecular Partners (CH)	pre-clinical	Amgen (US)	WW	44.1	482.0
BAN805	Parkinson's Disease	Bioarctic (SE)	pre-clinical	AbbVie (US)	WW	43.9	706.9
BC Lispro; BC Combo	T1D; T2D	Adocia (FR)	phase 1b/2	Tonghua Dongbao (CN)	CN, certain other countries	41.3	111.5
CF Portfolio	CF	Galapagos (BE)	phase 2	AbbVie (US)	WW	39.5	214.9
Estelle	Contraception	Mithra Pharma. (BE)	phase 3	Gedeon Richter (HU)	EU excl. BE/LU, RU	35.0	55.0
vamorolone	DMD; 3 Add. Indications	Idorsia (CH)	phase 2b	Santhera (CH)	WW excl. JP/KR	30.7	421.5

Tab. 11. Top 10 out-licensing deals in 2018, by cash upfront amount (our universe)

Product(s)	Indication(s)	Out-licensing Company	Clinical Stage	In-licensing company	Territories	Max Total (mEUR)	Cash Upfront (mEUR)
IPH52; IPH4301: IPH-Siglec-9; 2 Other PC targets	Solid Tumors; Lymphoma; Melanoma	Innate Pharma (FR)	pre-clinical	AstraZeneca / MedImmune (UK)	WW, co-promotion option for EU	3832.8	60.1
ARGX-110; cusatuzumab	AML; MDS	argenx (BE)	phase 1/2	Janssen / Johnson & Johnson (US)	WW, co-promotion option for US	1585.2	264.2
OSE-172; Effi-DEM	Solid Tumors	OSE Immuno. (FR)	pre-clinical	Boehringer Ingelheim (DE)	WW	1115.0	15.0
OXB-102; AXO-Lenti-PD	Parkinson's Disease	Oxford Biomedica (UK)	pre-clinical	Axovant Sciences (US)	WW	715.3	25.5
BAN805	Parkinson's Disease	BioArctic (SE)	pre-clinical	AbbVie (US)	WW	706.9	43.9
imeglimin; PXL008	T2D	Poxel (FR)	phase 2	Metavant / Roivant Sciences (CH)	EU, US, WW excl. Asia	528.8	28.5
MP0310	Cancer	Molecular Partners (CH)	pre-clinical	Amgen (US)	WW	482.0	44.1
MOR106	Atopic Dermatitis	Galapagos (BE) / Morphosys (DE)	phase 2	Novartis (CH)	WW	472.5 each	47.5 each
4 TCR targets	Cancer	Medigene (DE)	research	Bluebird Bio (US)	WW	425.9	6.7
vamorolone	DMD; Up to 3 add. indications	Idorsia (CH)	phase 2b	Santhera (CH)	WW excl. JP/KR	421.5	30.7

Tab. 12. Top 10 out-licensing deals in 2018, by total deal value (our universe)

The deal for the co-owned molecule MOR106 was actually counted twice (once each for Galapagos and Morphosys, who both are in our universe), but listed only once in the tables. **The Top 10 (actually Top 11) out-licensing deals by cash upfront amount (Table 11) represented 705 mEUR or 80% of the 886 mEUR total cash upfront revenues from out-licensing deals in 2018. 4 out of the 5 deals with the largest upfront payments were in oncology.** The **majority of the deals (6/10)** with the

largest upfront payments were **for clinical-stage assets**, which is consistent with an increased value creation for deals signed at a later stage of development. To put things into perspective, if we look at the Innate's deal with AstraZeneca, this deal is actually for up to 5 pre-clinical assets, and not only 1, thus the inflated cash upfront. This is also the case for the Evotec/Celgene deal, which is a broad R&D and licensing agreement for multiple targets and candidates.

Another interesting metric is the percentage of the upfront amount (including cash and/or equity) as compared to the total deal value (let's name it U/T ratio). **The median U/T ratio was 7.7% (IQR = [3.9%-16.9%]) out of 26 out-licensing deals with all the contributions disclosed** (cash upfront amount, size of the equity investment when applicable, and total deal value). We will not show the data here but more than 90% of the out-licensing deals concerning pre-clinical assets (11/12) had an U/T ratio below the median, and 85% of the out-licensing deals concerning clinical assets (12/14, clinical and later stages) had an U/T ratio above the median. A simplified way to consider things is that the total deal value reflects the size of markets addressed by the licensed assets, while the U/T ratio reflects, on a first order, the stage at which the deal is signed. We will not show the data but the size of the upfront payment (cash and equity included) as a function of the total deal value clearly indicates an important gap between pre-clinical and clinical assets.

In addition, **5 out the 26 (19%) out-licensing deals with all terms disclosed included an equity investment, for a global amount of 255 mEUR**: 176 mEUR for Belgium/Netherlands (JNJ in argenx), 77 mEUR in France (AstraZeneca in Innate Pharma, Metavant/Roivant in Poxel, and Sarepta in Lysogene), and 1.6 mEUR in Germany (Oncologie Inc in Mologen).

The Top 10 out-licensing deals by total deal value (Table 12) represented 82% of the 13.1 bEUR of aggregated value of all the out-licensing deals. However, on a general note, the enthusiasm about the total deal amounts has to be tempered by the fact that typically, only a relatively small amount of the "biobucks" is actually booked by the out-licensing companies over the course of the deal. This can be explained simply by the high level of attrition in drug development (below 10% chances for a drug candidate entering in clinical development to get approved, on average [22]), and also by the fact that the juiciest milestones are usually linked to sales. Being eligible to record these sales milestones implies, first, that the licensed product gets approved in at least one major market - starting with the US-, and second, that the peak sales subsequently reach the sky-high projections. All in all, the multiplying odds usually lead to high discounts when modeling the potential earnouts from the out-licensing deals.

Interestingly, **3 out of the Top 6 out-licensing deals by total deal value were inked by French biotech companies in 2018. 4 deals in the Top 10 deals were in oncology**, and 2 for assets aiming at treating Parkinson's Disease. **Most of the deals (6/10) were for pre-clinical assets, all with global rights or global rights excluding Asia, or some Asian countries.** Of note, the 2 most important deals by deal value included a co-promotion option for one large market, highlighting the ability of the licensing companies to potentially secure a larger part of the upside when the stakes are high.

The cash upfront and total deal value data are represented on **Figures 43 and 44**, respectively, for the 2018 out-licensing deals. The large variations in the numbers are better visualized in log scale (y-axis). The large spread is explained by the small number of deals per country/cluster, and the large spread (standard error) in the amounts.

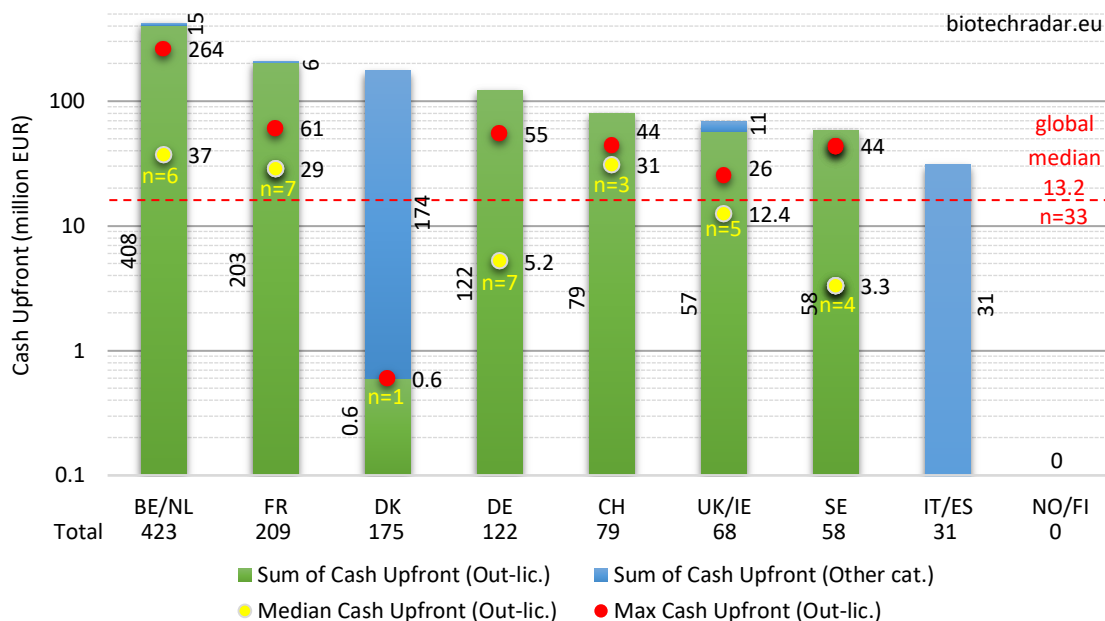


Fig. 43. Cash upfront amounts (mEUR) from out-licensing deals and from other categories, statistics for out-licensing deals, for each country/cluster in 2018 (disclosed upfront amounts from “n” out-licensing deals) – total cash upfront amount of 1.16 bEUR – N.B.1 equity investments excluded – N.B.2 y-axis in log scale

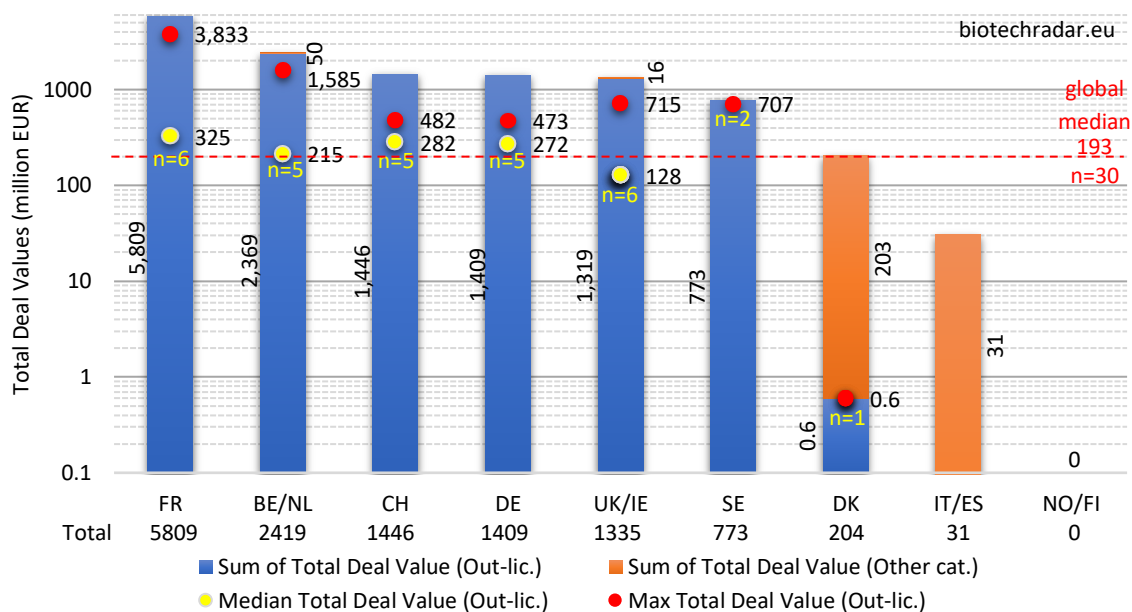


Fig. 44. Total deal values (mEUR) from out-licensing deals and from other categories, statistics for out-licensing deals, for each country/cluster in 2018 (disclosed total deal values from “n” out-licensing deals) – total of 13.4 bEUR – N.B y-axis in log scale

On **Figure 43**, one can see that the out-licensing deals logically predominated over the other deal categories, where the second highest contributions came from sales/divestments, consistently with the deal models mentioned on **Figure 41**. The **median cash upfront amount was 13.2 mEUR out of 33 out-licensing deal with a disclosed cash upfront amount**. Medians on small n’s (n≤2) were not calculated. Out-licensing deals with upfronts in the range of 50-60 mEUR in cash are statistically among the most important ones for European biotech companies, and even larger amounts are

outstanding deals. The success of Belgium/Netherlands is once again highlighted on **Figure 43**, with more than 400 mEUR of cash collected from upfront payments (all from out-licensing deals, equity investments excluded). France collected close to 210 mEUR, nearly all from out-licensing deals, followed by Denmark with 175 mEUR (royalties' stream sales by Zealand Pharma for 205 mUSD). 120 mEUR of cash went into the bank accounts of German biotech companies (all from out-licensing deals). Switzerland, UK/Ireland and Sweden all collected less than 100 mEUR in 2018 (79, 68, 58 mEUR, respectively).

In spite of the important out-licensing deal activity in the UK, as shown on **Figure 42**, the disclosed amounts of the cash upfront payments were globally below the European median for 2018. The highest cash upfront amount (26 mEUR) was also the lowest in the UK, if we exclude Denmark. Overall, UK/Ireland underperformed in 2018 on this metric. The same conclusion may apply for Sweden. The high number of companies and assets in active clinical development in these countries (see **Figures 9, 11, 16, 17**) did not translate in important cash inflows from out-licensing in 2018. A first reason is that, on average, the deals from companies in these countries were signed at earlier development stages (mostly preclinical or early-stage), as compared to the rest of the field. A second factor can be a relatively lower attractiveness of the assets available for partnering, as compared to the rest of the field, concerning the size of the markets, which would be supported by data from **Figure 16** (lower number of indications per assets). It also makes sense that companies willing to partner at very early stages (discovery/preclinical stages), mainly for financing reasons, cannot create a significant value from multiple programs per asset.

The total deal values per country/cluster are shown on **Figure 44**. In terms of methodology, this chart includes two kinds of data. First, those from deals for which the total amounts were disclosed. Second, those where only the cash upfront or total milestone amounts were disclosed. In this case, we used the disclosed amount for the total deal value. Consequently, the aggregated amounts naturally underestimate the actual total deal values. For the medians, only out-licensing deals with disclosed total deal values were taken into account.

For the total deal values, France took over from Belgium/Netherlands, notably thanks to the Innate Pharma/AstraZeneca multi-asset deal in oncology in the fall last year (total deal value close up to 4 bEUR). Two deals from the Top 10 (**Table 11**) also contributed for France's performance on this metric: one from OSE Immunotherapeutics (in oncology), and one from Poxel (out-licensing of a new class of agent for T2D for Europe and the US, and almost ready for a pivotal program). In contrast, Belgium/Netherlands only had one other deal in the Top 10, in addition to the argenx/JNJ deal. As shown on **Figure 43**, Switzerland, Germany and the UK ended more or less in the same range (1.3-1.5 bEUR). There were no disclosed data from out-licensing deals for Italy/Spain, and no out-licensing deal at all for Norway/Finland. Only one event was recorded for Denmark, but the deal terms were only partially disclosed. **The median out-licensing deal size (all terms disclosed) was 193 mEUR**. In agreement with previous observations, the median total deal value in the UK (128 mEUR) was also lower than the European median. Though, the highest total deal value from Oxford Biomedica's gene therapy was the 4th largest in 2018.

Finally, we will conclude this section with the profiles of the companies who in-licensed assets from the European biotech companies in our universe, as shown on the different pie charts of **Figure 45**.

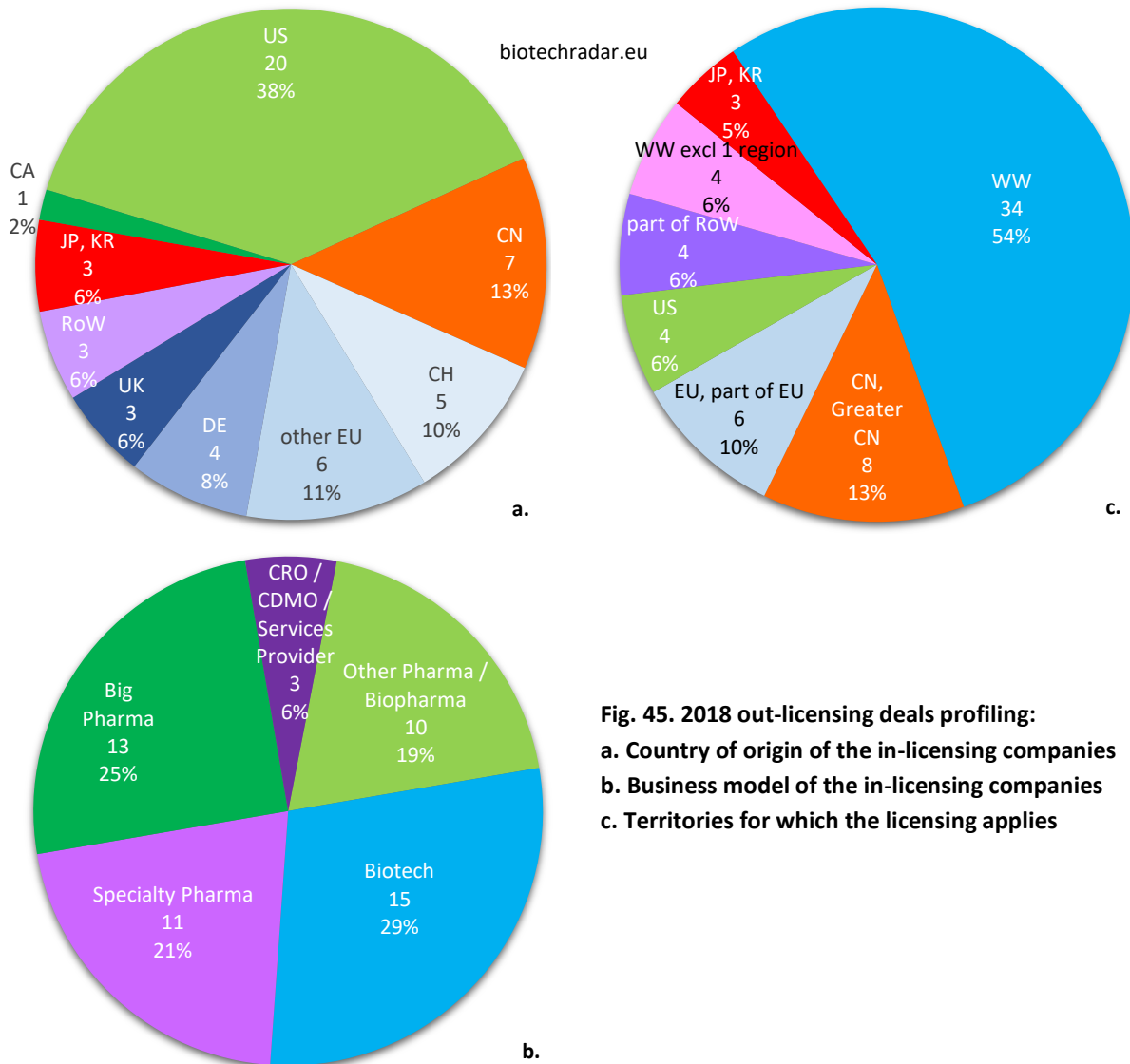


Fig. 45. 2018 out-licensing deals profiling:
a. Country of origin of the in-licensing companies
b. Business model of the in-licensing companies
c. Territories for which the licensing applies

Out of 52 out-licensing deals, **40% were signed with companies from North America, predominantly from the US (Figure 45.a.)**. 35% of the deals were inked with European companies, including 25% from German, British and Swiss companies (only 1 deal each from France and Spain, none from Italy). 10 deals (19%) were contracted with Asian companies, including 7 (13%) with Chinese companies. Thanks to the regulatory changes in China over the past few years, **a potential deal megatrend has been initiated between Europe and China/Greater China**. Indeed, the “innovative drug” definition is broader in China [23-24]. The appetite from Chinese companies for affordable assets to serve their domestic market is an opportunity to monetize some assets for companies worldwide. However, the deal amounts (upfront and total deal value) are usually very modest. The Adocia/Tonghua Dongbao deal, ranked 7th in the Top 10 by deal upfront amount in 2018, is clearly an outlier. Only few deals (6%) were signed with companies from the “Rest of the Word”. Their contribution is more important for supply/distribution deals, when companies try to maximize their revenues through regional deals, usually post-approval.

For the category of the in-licensees (**Figure 45.b.**), data are somewhat well balanced. The in-licensing companies were **“Big Pharma” (Top 20/Top 30 companies by market cap) for 1 deal out of 4**.

However, the most important contributions came from the “Biotech” segment (29%). “Specialty Pharma” companies, small or large, picked some bolt-on assets to represent 21% of the in-licensees. 19% of the in-licensees were from “Other Pharma / Biopharma” companies, including pharma/biopharma companies outside the Top 20/30 (this category may include some large biotech companies as well). A marginal contribution from “CRO / CDMO / Industry Service Providers” was also recorded. The relatively weak data from “Big Pharma” companies, who have the highest “fire power” for in-licensing deals, can be explained by a high level of requirement when picking assets, chasing mainly for the next potential blockbusters. This leaves a broad range of opportunities for the other companies in general, and principally for those with the financial means, among the “Other Pharma / Biopharma” and “Specialty Pharma” companies. The companies also need to find new assets to fill their pipeline and product portfolio, but without the necessity to hunt for a blockbuster. Indeed, they will preferably select assets for which they can handle the marketing and commercialization, fitting with their scale, strategy, and positioning. Overall, the “Big Pharma” companies are the lions of the biotech savannah: they bite first -but cherry-pick-, the rest can only eat when they are done.

Lastly, **more than half of the territories (54%) for which rights were granted** from out-licensing deals were concerning **global rights (Figure 45.c.)**. This proportion **raises to 60% of the territories if we add the worldwide rights excluding one region**. The numbers for Asia (18%) are almost the same as the country of origin of licensees (19%), which means that the companies from these countries typically only look for rights for their domestic countries, as we already mentioned. The split between China and Japan/South Korea is also the roughly same. The last 28% of the territories negotiated included the rights for Europe or a part of Europe (10%), for the US (only 6%), and for the “Rest of the World” (also 6%). **74% (17/23) of the deals signed with “Big Pharma” or “Other Pharma / Biopharma” companies were for global rights (“WW” category only)**, the remaining 26% were relating to deals for China/Greater China. 73% (11/15) of the deals with “Biotech” companies were also for worldwide rights. In contrast, only 18% (2/11) of the deals signed with “Specialty Pharma” companies were for global rights. In conclusion, the licensing of global rights remains the preferred option for the out-licensing companies, and for the in-licensing companies with important financial means, even within the “Biotech” segment. This is much less the case with companies with a more focused business model like the “Special Pharma” companies. Therefore, the total deal values are also much lower with companies from this category.

8. Portrait of a “typical” biotech company listed in Europe

The **Table 13** displays a snapshot of a “typical” biotech company listed on the European markets, at the end of 31/12/2018. The data rely mainly on medians of the metrics introduced in this review.

<p>Inception: 2003</p> <p>(median)</p>	<p>biotechradar.eu</p> <p>Employees/FTEs: 30</p> <p>(median)</p>
<p>EU Listing: 2011-2014</p> <p>(median listing date - median inception date plus median inception-to-listing period)</p>	<p>Market Cap: 72 mEUR</p> <p>(median)</p>
<p>Pipeline: 1 late stage asset, 1 early stage asset, no commercial product</p> <p>(est. based on the pipeline of companies in a range around the median market cap)</p>	<p>R&D programs in active clinical development: 4</p> <p>(median of R&D programs of companies in a range around the median market cap)</p>
<p>Cash Position: 17 mEUR</p> <p>(median, as of 31/12/2018)</p>	<p>Cash Runway: 13 months</p> <p>(median, based on our 2019 cash burn estimates for each company)</p>

Tab. 13. Portrait of a “typical” European listed biotech company, as of 31/12/2018.

9. Conclusion

This introductory review of the public biotech landscape for 2018 provided a comprehensive overview of the main characteristics of this landscape, both at the European and at the country levels.

We selected 150 listed companies into our core biotech pool, from the main European stock markets. Unsurprisingly, this selection mainly consists of small companies by the size, and also by the market capitalization. We saw that almost 60% of the listed biotech companies in our selection had either reached the commercial stage (by themselves or with a partner), for 21% of them, or were at late stages of development (38%). We believe that this is a higher proportion than those who follow the European sector would think.

We also assessed the breadth of the R&D pipeline in Europe and for each country/cluster, highlighting e.g. more than 100 unique programs in phase 3 (running or just completed as of 31/12/2018).

While French listed biotech companies were displaying interesting pipeline characteristics overall, the picture was much more contrasted for the British biotech companies. Indeed, a series of clinical failures and negative news had the UK sector's biotech stocks to be cut by half, on average.

We also pointed out a relatively early-stage landscape in Sweden, even if Sweden hosted the largest number of listed companies in Europe at the end of the year. Overall, 2018 was rich for the Swedish sector, with one buyout, and especially in the second half, with the fire started during the summer by BioArctic. However, it will probably face an important challenge in a near future: how to feed all these companies with cash? The situation could remain manageable as long as the ecosystem remains relatively "early-stage", but it might become much more challenging then.

The German sector characteristics are mainly driven by 2 R&D powerhouses, Evotec and Morphosys. This is the same for the Danish sector with the largest European biotech company, Genmab.

The Belgian/Dutch biotech sector is the major in the class, without delivering impressive pipeline indicators, but clearly yielding outstanding performances as compared to the other countries. Galapagos and Ablynx broke out over the past few years, followed by argenx, and also Mithra in 2018. Moreover, this good momentum was materialized by 2 buyouts of Belgian biotech companies.

Conversely, we saw that the Swiss sector, despite a restricted number of companies, still presented good indicators, especially on the late-stage profile of the companies and the qualitative figures of their pipeline. Nevertheless, it did not prevent the stocks of the Swiss biotech companies to follow the same down trend as everywhere else in Europe in 2018.

Finally, we found almost diametrically opposed characteristics for the Southern Europe cluster (Italy and Spain), and for the Nordic cluster (Norway and Finland). The common points were the small number of companies in each cluster and undifferentiated stock performances in 2018. But Italian and Spanish companies have a much more mature profile than in the Nordics.

Based on these different national dynamics, 3 main stocks markets dominate in Europe: Euronext, well helped by the Belgian and Dutch ecosystem, much less so by the French one; Nasdaq OMX, relying on both a large offer in Sweden build over the past few years, and an established place like

Denmark, home of the largest European biotech; and finally Deutsche Börse/Xetra, mostly relying on an historical list of biotech companies, including 2 large “platform” companies, whose success lies in their drug discovery engines and expertise.

In terms of IPO activity, the discrepancy between the “IPO boom” in the US and the gloomy numbers in Europe for 2018 was striking, denoting 2 opposite sentiment trends.

On the financing environment, the signals were mixed for the biotech sector on the European markets, since the total funds raised in 2018 (3.6 billion EUR) declined approximately by 15% from 2017. A decline almost only due to the low amounts raised from IPOs (-1.1 billion EUR). Interestingly, the funds raised from secondary offerings and directed issues -including equity investment from partners- even progressed in 2018 (+600 million EUR or +37%), partly offsetting the poor IPO numbers. More generally, in Europe, there is a systemic imbalance between the availability of financing for the biotech companies, and the growing needs. In such, having seen so many IPOs on the past 5 years might just have exacerbated this imbalance. Obviously, the situation might be different from one country to another, however global concerns remain. Solutions have yet to be found, unless a natural selection process occurs, with the “survival of the fittest”.

Lastly, we reviewed the 2018 deal flow. Out-licensing deals allowed approximately 1 company out to 5 to monetize some preclinical or clinical assets, for nearly 900 million EUR of cash inflows, and for almost 1.2 billion EUR including sales and divestments. These amounts represent a nice -and needed- extra, as compared to the financing numbers. Moreover, the momentum on the Europe/China deal axis will be interesting to follow in the coming years.

In conclusion, the European biotech sector exhibits very different characteristics from country to country, a bit like Europe in general, united but not unique from cultural or political standpoints. Unfortunately, there was a common point in 2018, which was the negative trend in terms of biotech stock performances in Europe, with only few national sectors outperforming. In such, the Belgian and Dutch sector was clearly identified as a stronghold in Europe over the past few years.

While a few companies, the “chosen ones”, are expected to show the way to success to their little sisters, a virtuous circle has yet to start. This is also why the sector needs success stories and companies who remain independent. The European sector needs to build on a larger community of specialized and educated investors, who understand the codes of this technical sector, and are less discouraged than the retail base by the attrition inherent to drug development.

So far in 2019, the long-term sector sentiment on the European markets is still following the descending part of a hype cycle (dismal IPO figures year-to-date), and it is unsure yet if the inflection point is close, or reached. We will not provide any 2019 data here, since we will release some in the coming weeks on biotechradar.eu, following the release of this review. However, the market data for Europe, also available on our website, clearly indicate mixed stock performances year-to-date, despite a runup period at the beginning of the year across the board. A déjà vu, so that as of today, it is not even certain that 2018 was a bottom year for European biotech stocks. Anyways, 2019, we already know that, will be a year of superlatives for the European listed biotech sector.

Like in the introduction, we will end this review by a small list of questions, starting with 2019. Will most of the European sectors recover in 2019, and especially the British sector? Will Sweden sustain

the positive trend seen in 2018? How will the smallest clusters do? Will the financing environment confirm the few positive signs observed in 2018 or will it deteriorate? Will the pool of companies of the “billion EUR biotech club” keep growing? Will we see positive signs on M&As, IPOs, deals?

And on the mid- or long-term. Will the Belgian/Dutch sector “convert the try” at the commercial stage? Will the French biotech sector eventually find a leading company that can drag the sector up? How will the Swedish sector be funded in the future? Can the German sector be renewed, and how will the 2 leading companies do in the future? Can Idorsia follow the same path as Actelion? Can Genmab be an even brighter star, and can the company build on other successes than Darzalex? Could Southern Europe become a new hotspot? Will the Norwegian companies get a new breath after the premises of the past few years?

Potential answers on biotechradar.eu, in further communications from us.

A vast majority of the company level data consolidated in this review are available on our intelligence service (subscription service for pro only). We provide small granularity data, and insights on the main items of biotech investing, for more than 150 companies listed on the main European markets. Disclaimer: we do not provide any investment recommendation on our service. This review is not aimed at supporting an investment decision on any company, any country, or any stock market mentioned in this report. See more details on biotechradar.eu.

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2018 Fact Sheet

- **150 European biotech companies in our universe**, from **13 European countries**, and listed on stock markets from **8 operators**
- **1 company out of 5 in our selection with at least one product generating revenues**, **38% in “late-stage”**, **27% in “early-stage”**, rest at preclinical stage
- **341 unique product candidates in active clinical development (57 in phase 3)**, **76 unique commercial products**, **624 R&D programs in active clinical development (105 in phase 3)**
- **43.8 bEUR of total market capitalization**, and **median market cap of 71.7 mEUR at the end of 2018**, versus **391 bUSD of total market capitalization for a selection of US biotech listed on Nasdaq**, with a **median market cap of 194.2 mUSD**
- **Nasdaq OMX and Euronext as the main stock markets at the end of 2018**, each representing one third of the total valuations, **LSE/AIM clearly lagging**
- **8 European companies with market cap ≥1 bEUR at the end of 2018 (9 in USD)**, **84 out of 503 selected companies on Nasdaq with a market cap ≥1 bEUR (89 in USD)**
- **-17% average and -29% median for the stock performance of 155 European biotech companies (of which 5 de-listed) in 2018**, roughly **-50% for UK biotech stocks (average and median)**
- **244 mEUR daily average turnover on the biotech sector in Europe**, **84.3% of the turnovers concentrated into the 3 main European markets by total market cap (Euronext, Nasdaq OMX, XETRA)**
- **Approximately 15500 employees or FTEs among our 150 European listed bios at the end of 2018**
- **3.62 bEUR raised from financing activities in 2018 (-15% year-over-year)**, including **2.3 bEUR (+37% y-o-y) from “offering”-like financing**, **median amount raised of 8.9 mEUR from offerings/issue of equity in Europe** versus **17.5 bUSD (~14.8 bEUR) in the US for “Follow-On Public Offerings”**
- **4.6 bEUR of cash collected in 2018 including 0.97 bEUR from extra sources of cash (sources outside financing activities, including licensing deals mainly)**
- **72% decline in amounts from US IPOs (dual listings)**, **67% decline from European IPOs**
- **A tremendous gap in IPO dynamics between the EU and the US in 2018**
- **3.29 bEUR of total cash burn**
- **35% of the companies with less than 12 months of cash runway at the end of 2018**, **65% with more than 12 months**, **one third with more than 24mo of cash runway**
- **Median of 75% of the total operating expenses allocated to R&D**
- **52 out-licensing deals**, including **886 mEUR of cash upfront payments**, for a total value of **13.1 bEUR - 1.16 bEUR of cash collected** and **total deal value of more than 13.4 bEUR**, all deal category included
- **Median Upfront Amount/Total Deal Value ratio of 7.7% out of 26 out-licensing deals with all the contributions disclosed**, of which **5 (19%) including an equity investment**, for a global amount of **255 mEUR**
- **Median cash upfront of 13.2 mEUR out of 33 out-licensing deal with disclosed data**, for a median total deal value of **193 mEUR**
- **A potential deal megatrend initiated between Europe and China/Greater China**

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Annex 1

This annex refers to the introduction of a simple reference model of the cash raised over a year for a group of “n” biotech companies, whose market caps are known.

To explain how we defined this reference, one has to understand the cash needs of companies and how much each company may typically be able to raise over a year, on average. To briefly describe these needs in both qualitative and quantitative ways, the smallest companies usually raise small amounts (generally few units of mEUR, couple of tens at best) but frequently (once a year or more). The largest companies raise much larger amount (several tens of mEUR and sometimes >100 mEUR for the top companies), but potentially less frequently: indeed these companies may have revenue streams offsetting partly their needs, and they are able to raise larger amount at better costs of capital, because of an increased visibility on their business, as compared to the rest of the field (reflecting, normally, a higher level of de-risking). So basically, each raise provides them with increased runways, and they are much more well-funded, even if this relative ease to raise funds is variably offset by higher cash burn rates. Finally, the companies with a market cap in a broad range around the median (those we call “typical” biotech companies) also regularly need cash, but not every year like smaller caps but rather more frequently than the largest companies. The “typical” companies, statistically speaking, raise larger amounts than the smaller caps (around ten, or few tens of mEUR, as previously indicated by the median equity raise of 8.9 mEUR and the 3rd quartile boundary of 22.0 mEUR). To summarize, the amounts raised by the companies are linked to their market caps, which are distributed in a non-linear scale, as shown on **Figure 19**. They also depend on the frequency at which the companies are likely to raise money.

Based on these elements, the idea is to see if one would find a simple correlation between the amounts raised by a pool of company and data characterizing that pool. The simplest approach we propose is the following:

$$\text{Amounts raised} = \frac{(n * \text{median market cap})}{K}, \quad K = \text{constant (fit parameter)}$$

Where we link the amounts raised over a year to the median market cap at a time to be defined (we tried with the end of the year – see limitations below), and to the number of companies, divided by a constant K. This is equivalent to consider that the largest companies in a pool do not need to raise much money because they are well funded, or if they do, by highly discounting their contribution (lower frequency and low number of companies). This is also equivalent to neglect all the small amounts from the smallest companies, with respect to the amounts raised by the “typical” companies. And finally, the constant divider K would reflect a sort of typical integrated percentage of companies who need to raise money over a year, also taking into account a mix of biases implied by such a simple approach.

By pushing a little further, we found a better correlation with the 60-th percentile of the market cap (at the end of 2018) instead of the median (50-th percentile), with R²=0.81 versus 0.65, respectively, for linear regressions performed on the proportions of cash raised per country (**Figure 46**). This shift towards a higher percentile might reflect a slightly higher overweighting of the amounts raised by the companies around this percentile (approximately 100 mEUR according to **Figure 19**), as compared to the smaller and the larger caps.

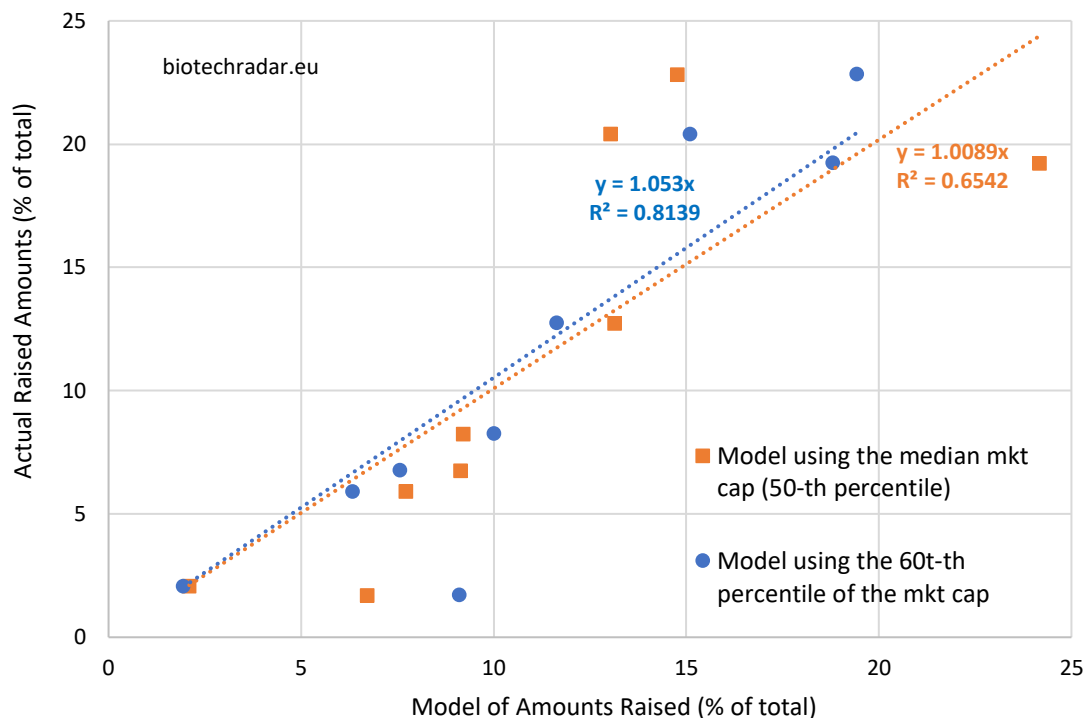


Fig. 46. Comparison of actual amounts versus model estimates, for the cash raised by each country/cluster in 2018, using the median or 60-th percentile of the market capitalization of each country cluster (end of year data)

One can also add that the companies into an advanced process of transition towards the integrated pharma-like business model do not even need to raise money anymore since they usually generate net positive cash flows (net benefits). Therefore, a bell shape can be expected in terms of amounts raised versus the market cap range.

Of course, this simple model only provides indicative values, and has important limitations. First, the samples in some countries/clusters are relatively small, limiting the accuracy on the n-th percentile lookup. Then, the financing operations occur over a defined time window, and we only compute our model with data extracted at one point in time (at the end of the year). It would indeed make more sense to establish this model with respect to weighted averages over the year (if computed a posteriori), or better, at the time of the events. For prospective estimates, the only choice would be to use the market cap data at the beginning of the year (given that 2018 was a negative year, it would not be surprising that the model using the median at the end of 2017 would provide decent estimates). Finally, we have not excluded any operations in 2018 that could be considered as “outliers”, even if we previously quoted a few operations “driving” the numbers in one direction or the other for some financing categories. Notably, the top 5 largest companies in our selection can easily impact the numbers up (e.g. the recent Genmab US IPO, likely to represent 5-10% of the total financing amounts in 2019). So, one should expect significant year-to-year variabilities with respect to the reliability of this simple model. Also, we did not “backtest” this model with datasets from other years, so we cannot even say what we validated it. In conclusion, this model is an exploratory work. It provides only a rough idea of the amounts raised by countries, but has the merit to link these numbers -that could appear relatively random otherwise- with parameters that can be easily extracted or computed.

Annex 2

This annex refers to a “tentative” data reconciliation aiming at established a relation between our method to calculate the cash burn amounts of the companies, and the financial data from the income statements.

The linear regressions performed indicate on **Figure 47** a linear relation of the cash burn with both the operating result, and another simple model proposing to compute the “OpEx - (Sales of Products - Cost of Sales)” amounts. While using the operating results leads to an underestimation of the cash burn amounts, an overall better fit is obtained with the second model (“custom formula”), which given our definition of the cash burn not taking into account the recurring contributions, seems more accurate. However, this second model overestimates the cash burn amounts. The reasons leading to a deviation by 23% of the ideal slope ratio of 1 have yet to be elucidated.

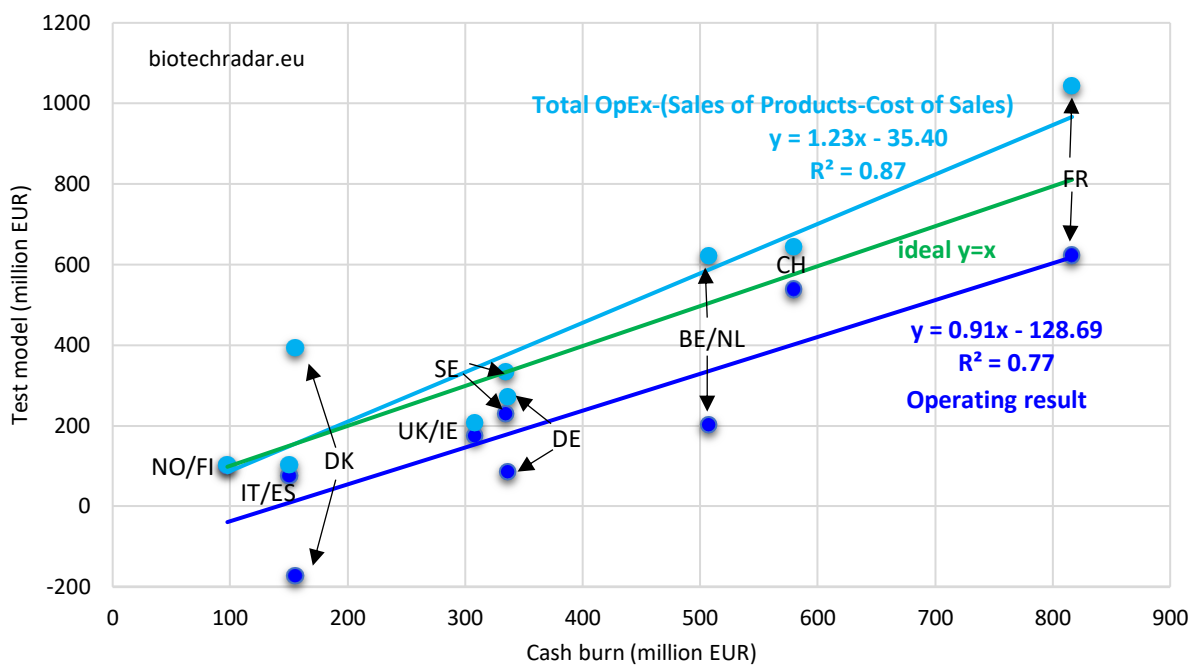


Fig. 47. Relation between cash burn, operating result, and a custom formula – data by country/cluster

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