The EU General Pharmaceutical Legislation & Clawbacks:

Calculated impacts – both designed and unintended.

April 18, 2024

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Executive Summary:

European competitiveness in the innovative healthcare sector is facing increasing global challenges from both established competitors such as the United States, as well as emerging economies such as China. It is important for the future of the European Life Sciences sector to optimize policies to promote innovation, job growth, and access to new medicines for European patients. Unfortunately, our study sees an accelerating decline in several European life science key performance indicators within the EU.

In particular, the combination of unsustainable "clawback" policies that require companies to pay back revenues resulting from arbitrary budget limits, as well as proposed reductions in IP protection undermining direct incentives for innovation upon which life sciences companies rely, threatens to accelerate an already negative trend which puts the European life sciences ecosystem at a disadvantage with the United States. Our study finds a profound decrease in revenues, the creation of fewer EU biotech companies, the movement of investment flows out of Europe, and the development of fewer EU innovated medicines.

Further, these policies will incentivise emerging global life sciences challengers such as China.

For example, the European Commission has proposed that the revised General Pharmaceutical Legislation will replace the current base of 10-years of regulatory data protection with a base of 8-years. The General Pharmaceutical Legislation then provides for a series of carrots and sticks to act as incentives for investors, innovators, and industry to 'improve' EU biopharmaceutical innovation, and gain back those lost years of regulatory data protection. As well, under some scenarios, innovators may have the ability to extend regulatory data protections to 12 years.

The challenge for investors and drug developers regarding the potential risks created by two years of lost regulatory data protection is that there is never a 100% certainty that patent protection alone will satisfy the length of time to develop a drug. Shortening RDP will increase risks on the investments required to bring a drug to market, and further exacerbate the competitive disequilibria currently seen between the U.S. and EU biopharmaceutical innovative sectors.

Shortening regulatory data protections will leave investors unsure if they will be exposed to more regulatory changes and risks, after they have undertaken an investment which, at minimum, will take 10 years on average before the EMA grants a new drug's approval.

In relation to clawbacks, the situation is entirely unsustainable, where actual revenues would be eclipsed by the obligated pay back mechanisms if current trends remain unchanged.

This study outlines the following core findings:

Impact of Reducing Regulatory Data Protection

From our cohort of 25 EU invented drugs, we find that 2 will be directly impacted by 24 months of lost regulatory data protection (RDP), with a total fiscal impact of -€1.22 billion Euros ($1.3 billion USD).

However, the European Commission has estimated that over 30% of all current EMA approved therapies will see revenues impacted by reducing RDP by 2 years; modelling our cohort to meet these criteria we find a 15% drop (-$64 billion) in total EU revenue in our 24-drug cohort, measured in constant 2013 $USD.

Impact of Clawbacks

The growth rate in member state clawbacks currently exceeds that of annual sales in our cohort by roughly 20% per year; assuming no changes in member state policies, total clawbacks will exceed our 24 drug cohort's sales revenues by the year 2033.

Cost of Proposed Measures Needed to "Regain" RDP

Assuming every company in our cohort were to exercise the incentive to seek market access in all 27 EU member states to obtain a further two-years of RDP, we calculate a total NPV loss in our cohort of over $400 million USD.

Assuming every company in our cohort were to exercise the opportunity to seek all available incentives to gain 12 years of RDP, we conservatively calculated a total NPV loss in our cohort of over $1.2 billion USD, we assume the actual results of this cost scenario will be substantially worse.

Impacts of Proposed GPL Changes and Clawbacks on European Competitiveness

The decline of European Life Sciences competitiveness began accelerating in 2018, driven at least in part by the global impact of US Corporate tax changes. Adding market uncertainty with changes to RDP will negatively impact the EU biopharmaceutical ecosystem and further accelerate its decline in relation to the US and other global competitors.

The RDP reduction through proposed amendments to the GPL projects a decrease in EU biotechnology startup firms from 19 in 2024 to 4 in 2030. Subsequently, there is a drop in biotech investments from roughly $18 billion USD in 2024 to $14 billion USD in 2030. These projections elevate the EU's biopharmaceutical market ambiguity and incentivize investors to move capital outside of the EU where there is less risk and RDP is more favourable.

Finally, the incentive measures needed to restore the lost years and/or provide additional regulatory data protection included in the General Pharmaceutical Legislation require significant financial and operational resource allocation, with a very uncertain result within 24 months of EMA's approval. This study calls into serious question their practicality in improving access for patients to needed new medicines in all 27 EU member states or in arresting the continued marked decline in global EU biopharmaceutical sector competitiveness.

The data used in this analysis can be accessed here.

Introduction: The General Pharmaceutical Legislation (GPL)

On April 23, 2023, The European Commission adopted a proposal for a new Directive and a new Regulation to replace the existing general pharmaceutical legislation. Commonly referred to as the General Pharmaceutical Legislation (GPL), It's stated objectives are to:

- Make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines
- Enhance the security of supply and ensure medicines are available to patients, regardless of where they live in the EU
- Continue to offer an attractive and innovation-friendly environment for research, development, and production of medicines in Europe
- Make medicines more environmentally sustainable
- Address antimicrobial resistance (AMR) and the presence of pharmaceuticals in the environment through a One Health approach. [1]

From the standpoint of policy design, the GPL provides a series of carrots and sticks to act as incentives for investors, innovators, and industry to foster EU biopharmaceutical innovation.

According to the European Commission, the GPL's *raison d'etre* is that it will make Europe, "An attractive and innovation-friendly environment for research, development, and production of medicines . . . [and] will create this environment by promoting world-class innovation, governed by stable and consistent rules."

Vital Transformation (VT) has been asked by a multi stakeholder consortium to analyse the European Commission's GPL proposal, including its incentives, to determine the regulation's likely outcomes and consequences, both by design and unintended. This VT report outlines the GPL in the context of the EU's goals of promoting world-class innovation and 'stable rules.'

The EU's Declining Footprint in Global Biopharma

For much of the 20th Century, the Global Biopharmaceutical sector was based in Europe, which had long been dominant in the industry, holding over 2/3rds of global innovation. In fact, in 2009 academic Arthur Daemmrich of the Harvard Business School found that, "Between 1961 and 1980, firms based on the European continent invented and brought to market over sixty percent of new therapeutic molecules". However, that same study by Daemmrich also notes that, "By. . .1991, . . .firms in the United States were inventing over forty percent of new drugs . . .Germany's relative ranking slipped further after 2001."[2]

VT's study released in 2021, The Historical Impact of Price Controls on the Biopharma Industry, sought to quantify the drivers of the global competitive shifts that were occurring in the biopharmaceutical sector which had been noted by Daemmrich, in order determine to what extent this decline in EU biopharmaceutical innovation had continued, if at all.[3] Our research found robust evidence that the continued downward pressure on prices in the EU had directly led to declines in biopharmaceutical industry investments in the European Union relative to the United States. By 2019, late-stage venture capital funding in the European Union was just 3% of the level in the United States, and from 2003 to 2019, biotech investments in the United States increased sixfold, while they remained static in the European Union.[4]

More troubling, in 2020, the U.S. share of total annual biotechnology startup firms was roughly three times greater than the EU share, and VT had found a statistically significant relationship between the differential of net revenues and the percentage of emerging biotechnology firms that were started in the EU and US (Figure 1).

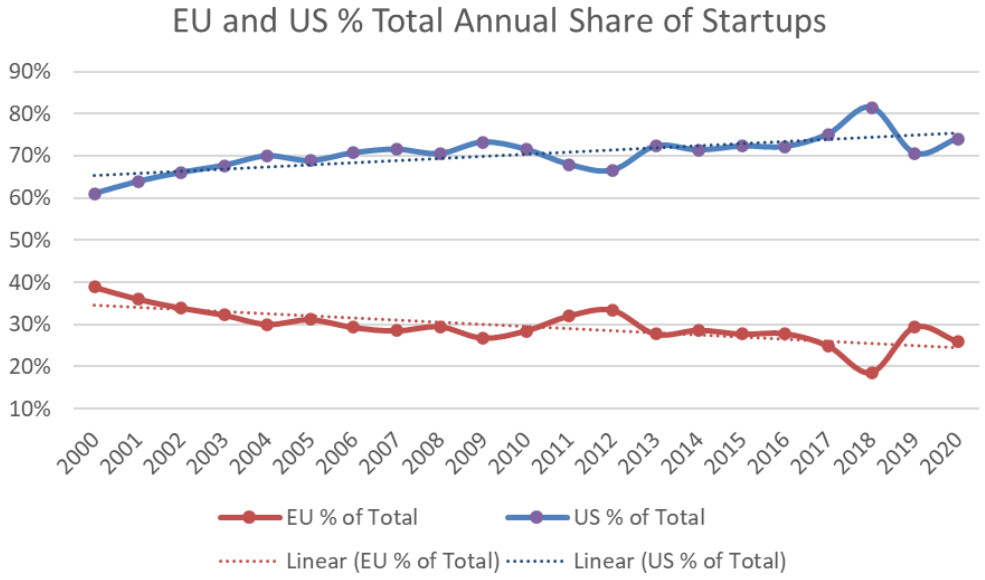

Figure 1 The US share of total startup biotechnology firms has grown; the EU share has declined. For every 10% reduction in the price of medicines in each market the number of biopharmaceutical firm startups in the EU relative to the US declined by 2% ($p < 0.01$)[5]

The operative questions are thus; does the GPL address issues that will impact the structural decline of EU biopharmaceutical sector competitiveness? Is this GPL the correct prescription for what is ailing the EU biopharmaceutical patient?

VT's methodology to analysing the GPL

Through a database obtained from IQIVA's Midas platform, VT extracted a cohort of the top 25* biopharmaceutical products by global sales over 11 years (2012-2022) that were invented in the EU, as determined via a drug-by-drug patent analysis. VT then obtained sales data for France, Germany, Italy, Spain, Switzerland, and the United Kingdom for the purposes of this study.

* One of the drugs in our cohort, although one of the top selling drugs globally, was not available in any of our EU country specific sales data, thus, our cohort is limited to 24 therapies.

Using this sales data, VT modelled the economic impacts of GPL both on their own and in combination with the increasing use of member-state revenue clawbacks which occur post-sale. We measured these impacts on the willingness of companies and investors to bring a drug to market, as well as other impacts of these policies. Our focus is targeted specifically upon:

- Biopharmaceutical company formation/investments
- Biopharmaceutical company NPVs, ROIs, and revenues
- Investor responses to incentives, market risks, and global regulatory changes

The stated overarching goal of the GPL is improving EU's biopharmaceutical sector competitive landscape. Given this, VT initially intended to restrict the research to therapies that were both invented in the EU and natively developed by EU-based industry by headquarter location. This type of research is facilitated by the fact that VT maintains a running database of over 350 EMA and FDA Type 1 approvals of novel therapies over the last 10 years, with links to all mechanism of action and composition of matter patents by point of origination.

Unfortunately, that search yielded only 17 therapies.

We opted instead to build our 25-drug cohort from drugs that were invented in the EU, regardless of the location of the developing industry headquarters. That search yielded 53 therapies from which we drew our sample of 25 novel patented therapies with the highest grossing annual global revenue.

It should be stated that from 60% of global biopharmaceutical innovation in 1980 being produced in Europe, the 53 therapies from our active database of 364 drugs approved over a 10-year period represents just 15% of the novel therapies in our dataset approved since 2011 having been invented in the EU. This is a truly stunning decline.

Using sales data from the top 25 selling therapies included in our 53-drug cohort, VT modelled the economic impacts of the GPL and member state revenue clawback provisions, to analyse and predict the willingness of a company to continue to invest in EU innovation.

At the heart of the GPL is the reduction by two years from the current 10-year base period of available regulatory data protection (RDP) to 8 years. The GPL then offers to innovator companies various opportunities, methods, and tools framed as incentives to recapture those lost two years of RDP. It is also at least theoretically possible to expand beyond 10 years and obtain a maximum of 12 years of RDP. However, many of these 'incentives' incur large upfront investments by a company, with no guarantee of success.

GPL and the regulatory toolbox: supplementary protection certificates, regulatory data protection, and market exclusivity in developing new medicines

The core question to be answered by this research is how much, if any impact the proposed changes to RDP included in the GPL will have on R&D investments in the EU? One must consider RDP in the context of the toolbox available to both regulators and innovators, as well as the vital roles they each play in creating the incentives to develop new therapies.

The success or failure of the GPL will be judged upon its ability to satisfy two realities:

- Certainty for investors putting capital at risk, often, for 20 years or more;
- Tractability in the approval pathway – does the GPL as it is designed improve and/or ease the ability of investors to bring a therapy to market?

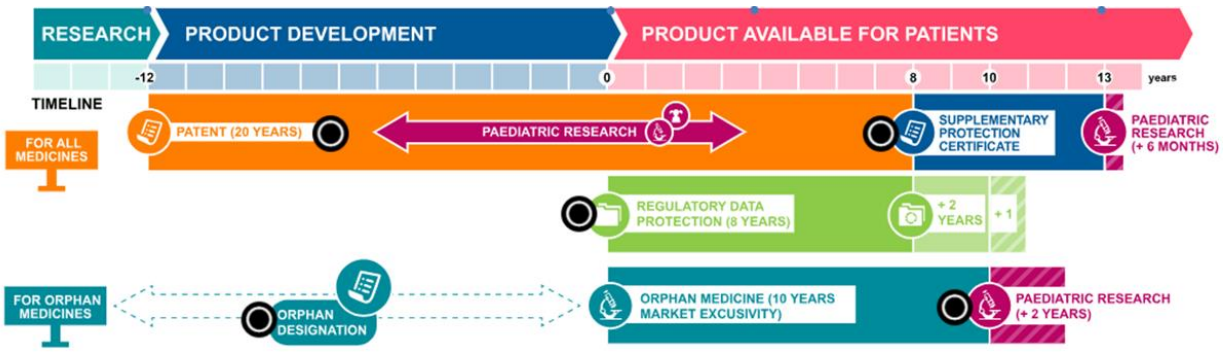

Figure 2 The European pharmaceutical incentives framework

As shown in Figure 2,[6] a drug is protected by overlapping regulatory pathways which create certainty for investors and developers to assume the risks of drug development. Primary is the patent of an innovation affording 20 years of legal protections. Given that the length of research and product development is often 6 – 10 years, a system of supplementary protection certificates (SPCs) was implemented whereby companies, upon obtaining market entry, can apply for an SPC term to restore patent time lost to fulfil regulatory obligations, so long as the term does not extend beyond 15 years measured from the date of marketing approval.

As well, once a new therapy is approved by the European Medicine's Agency (EMA), the marketed product is also allowed 10 years of RDP, consisting of a combination of 8 years of data exclusivity, with a further 2 years of market exclusivity. In short, during the 8-year period, a generic or biosimlar producer is not allowed to rely on the data of the innovator to support a follow-on marketing application. These producers may file such an application after the 8-year term but any approval for marketing must wait until the end of the 10-year term. These allow generic and biosimilar manufacturers to access regulatory data for research purposes to begin preparing manufacturing for market entry, upon the expiration of the SPC or RDP, whichever comes last.

The challenge for investors and drug developers regarding the potential risks created by a two-year lost in RDP, is that there is never 100% certainty that patent protection alone will satisfy the length of time to develop a drug. For example, Lecanemab (Leqembi), Eisai's recently approved drug to treat Alzheimer's disease, took 13 years to reach the market and is still not approved by the EMA. One of the therapies in our 24-drug research cohort, Lutathera (lutetium Lu 177 dotatate) (see Appendix), came to market with no patent protection. According to Advanced Accelerator Applications S.A., (the original developer of the therapy) when reporting in their Securities and Exchange Commission (SEC) 20-F filing in 2017, "the patents covering claims related to lutetium Lu 177 dotatate (Lutathera) have expired."[7]

Why would a company such as Novartis acquire rights to Lutathera and bring it to market in the EU on September 29, 2017, when its patents had already expired? The answer is that RDP, alone or in combination with an orphan designation, offers a vital line of certainty and tractability for investors

in cases where a lengthy development pathway has been undertaken, and the available patent life is shortened or, in the case of Lutathera, completely exhausted.

Often, effective but complex treatments, such as the radiotherapy Lutathera combining several different treatment paradigms, take longer to complete their clinical development. Shortening RDP will have the impact of increasing the uncertainty risks to investors bringing new therapies to market, and often this will be magnified for those treatments using new mechanisms of action like Lecanemab (Leqembi), which are exactly the needed novel innovations required to solve societal issues such as Alzheimer's Disease.

Reducing regulatory data protection will also increase the risks of developing combination treatments, where a known safety profile and longitudinal body of evidence for treatments is mandatory, and repurposed treatments where patents have expired in their targeting of new therapeutic areas. Shortening RDP will increase risks on the investments required to bring these drugs to market, and further exacerbate the competitive disequilibria seen between the U.S. and EU innovative biopharmaceutical sectors. As well, shortening regulatory data protections will leave investors unsure if they will be exposed to more regulatory changes and risks, after they've undertaken an investment which, at minimum, will take 10 years on average before the EMA grants a new drug's approval.

The link between revenue and R&D

According to John LaMattina, the former president of Pfizer Global Research and Development, "The pharmaceutical industry invests 25% of total sales into R&D... what is a company going to do with less revenues? When Lipitor went off patent... we closed research sites around the globe. Fewer researchers, and fewer research programs. Is this really what we want to do?"[8]

Recent data published by NYU's Stern School of Business (Figure 3) shows that the biopharmaceutical industry in 2023 spent, on average, 33% of its sales revenues on R&D (44% for biotech, 22% for pharma). This puts the entire biopharmaceutical sector, including biotechnology firms that primarily focus on biologics and larger pharmaceutical firms which traditionally focused

on chemically based molecules, well ahead of software and semiconductors at 21%, the next most intensive R&D sectors.[9]

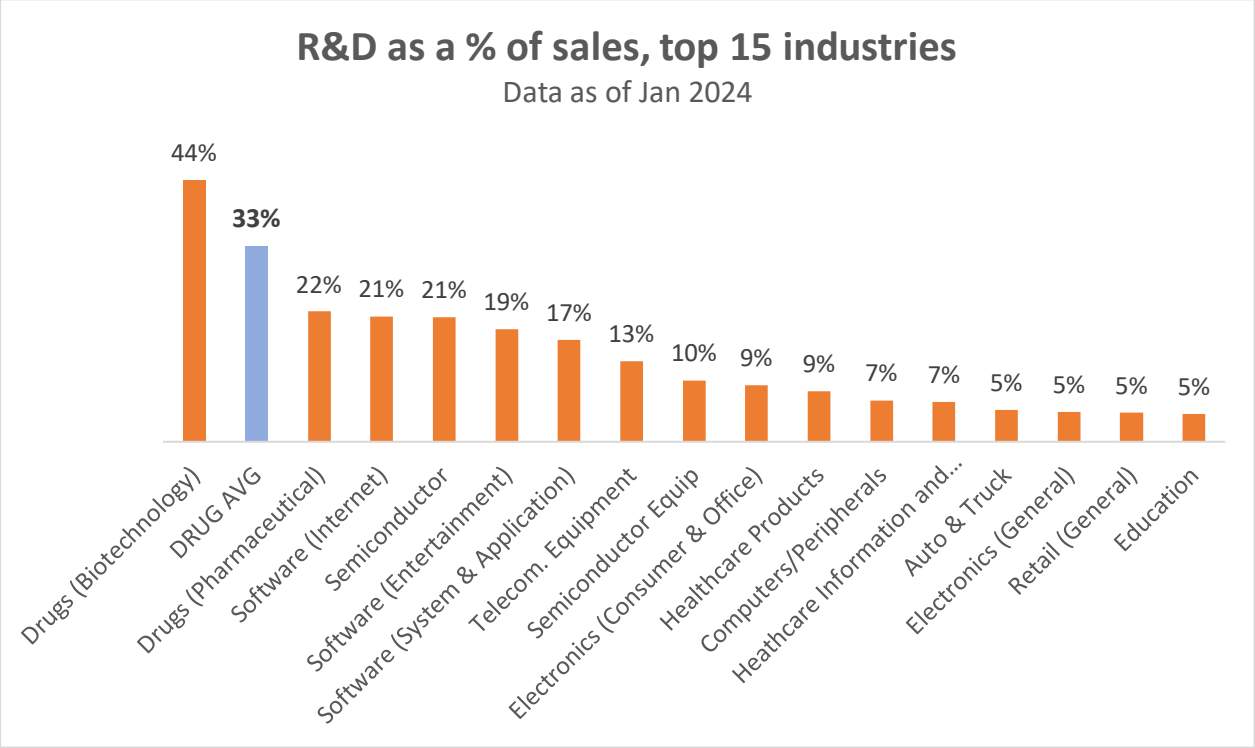

Figure 3 Source - NYC Stern School of Business

Using our drug pricing data for France, Germany, Italy, Spain, Switzerland, and the United Kingdom from the years 2012-2022, VT measured the changes in revenues which occurred in our 24-drug cohort and then determined the statistical impacts of revenue reductions upon KPIs vital to biotechnology development in the EU (Figure 4). For every 10% reduction in EU revenues, we see substantial losses in EU competitiveness as measured via these KPIs.

Our data indicates that market forces, i.e. revenue reductions, are a key metric in determining where and how much R&D occurs. Further, given the erosion of EU competitiveness compared to the U.S., increasing market ambiguity related to RDP while pricing pressure is also being applied to manufactures through member state clawbacks, will further increase risks for investors.

Biotechnology Market Indicator (per capita)	KPI impact per 10% reduction in EU sales	95% C.I.
Patents – Biotech ***	9.5%	7.67% – 11.24%
Patents – Pharma ***	9.1%	7.02% – 11.08%
R&D Pharma ***	9.0%	6.96% – 11.02%
R&D Biotech ***	4.6%	2.59% – 06.63%
VC Deal Amount Raised ***	9.0%	6.11% - 11.79%
Total VC ***	6.1%	4.98% – 7.21%
Seed VC ***	5.3%	3.56% – 6.96%
Early Stage ***	7.6%	4.65% – 10.53%
Late Stage ***	3.6%	3.10% – 4.05%

Figure 4 Impact of lost sales and price controls on EU KPIs, N = 66; *** p< 0.001

Estimates based on data for 6 countries (France, Germany, Italy, Spain, Switzerland and United Kingdom) over 11 years (2012-2022). All variables measured per capita, and in constant 2015 USD. Estimation assumes residuals exhibit contemporaneous correlation, heteroscedasticity, and AR1 autocorrelation specific to each country. Switzerland used as baseline comparator for elasticity calculations.

To quote former Citibank CEO Walter Wriston, who is credited with staving off New York City's bankruptcy in October of 1975, "Capital goes where it is welcome and stays where it is well treated."[10]

Proposed changes to regulatory data protection in the GPL

The European Commission has proposed that the GPL will replace the current 10 years of (8 + 2 (+1*)) RDP system to an 8-year system (6 + 2 (+1*)). During the "+2" years, generics manufacturers are allowed to begin clinical testing and apply for market authorization, where they have access to an innovator company's regulatory data to facilitate more rapid development of biosimilar and generic drugs when the period of patent and/or market protections lapse.[11]

The +1 year of additional market protection may be available in only those specific cases where a new therapeutic indication brings significant clinical benefit in comparison with existing therapies. This extra year is awarded on a case-by-case basis and is not guaranteed during a drug's development.

Vital Transformation has analysed all patents, approvals, SPC dates, orphan designations, and RDP/Bolar exemption dates in our 24-drug cohort (see Appendix) to develop an accurate assessment of the direct impacts of the proposed changes in RDP. We find that in this specific cohort, only two drugs will be directly impacted by RDP reductions, roughly 8% of the cohort. By "directly impact," we mean that RDP is the last exclusivity relevant to the product that will expire. For other products, some other type of IP protection, for example patents, mean that the shortened RDP period will not, *per se*, reduce the term of exclusivity.

Drug	Country	PV with Data Protection	PV with 2 years less Data Protection	Loss in PV per Country	Total Loss over All Countries	Total Loss as % of PV with Data Protection
EPIDIOLEX	FRANCE	€ 793,432,312	€ 325,503,727	€ (467,928,585)	€ (1,218,913,531)	-56.8%
	GERMANY	€ 749,672,898	€ 344,752,576	€ (404,920,322)		
	ITALY	€ 292,312,011	€ 124,776,688	€ (167,535,323)		
	SPAIN	€ 310,309,749	€ 131,780,448	€ (178,529,301)		
LUTATHERA	ITALY	€ 48,173,144	€ 46,773,035	€ (1,400,109)	€ (2,094,051)	-0.1%
	SPAIN	€ 39,135,418	€ 38,441,477	€ (693,942)		
Totals		€ 2,233,035,533	€ 1,012,027,951	€ (1,221,007,582)	€ (1,221,007,582)	-54.7%

Figure 5 Direct Impact of EU proposed 2-year reductions in RDP. All values in 2023 EUR.

When the impact of losses due to RDP are calculated (Figure 5), we find that Epidiolex will lose roughly €1.2 billion and Lutathera €2.1 million in revenues. However, what is not represented by these losses are the long-term unintended consequences created by the increased risks and market uncertainty caused by the threat of reductions to RDP.

When an investor begins developing a drug there is no way to know if that drug will eventually be treated like Epidiolex, i.e. one of the 8% of the therapies in our cohort that has revenues impacted by legislative changes more than a decade into the future. Altering data protections will be a strong market signal that investments may be at risk due to future regulatory changes, leading innovators and VC, particularly those who invest in early-stage drug development, to alter their behaviour even more than a decade in advance.

To quote VC Peter Kolchinsky, Managing Parter at RA Capital Management, "I worry about anyone who says it's just a one-time thing, it's not . . . [it's] the way you will treat my drugs someday, if not worse."[12]

Whilst our cohort analysis found only 8% of our test therapies impacted by RDP reductions, according to a recent European Commission assessment, roughly 30% of all EMA approved medicines will see reduced revenues with a 2-year reduction in RDP, when accounting for all treatments including combination therapies, multiple-indications, etc.[13] To simulate this impact, VT randomly selected 8 drugs from our cohort, representing roughly 30% of our treatment cohort as being impacted by RDP as outlined by the EU (Figure 6). Those drugs were Aptiom, Brilique, Briviact, Darzalex, Keytruda, Lutathera, Tradjenta, and Xarelto. Future revenues were simulated to account for two years' lost RDP, and sales were projected forward to the year of SPC expiration.

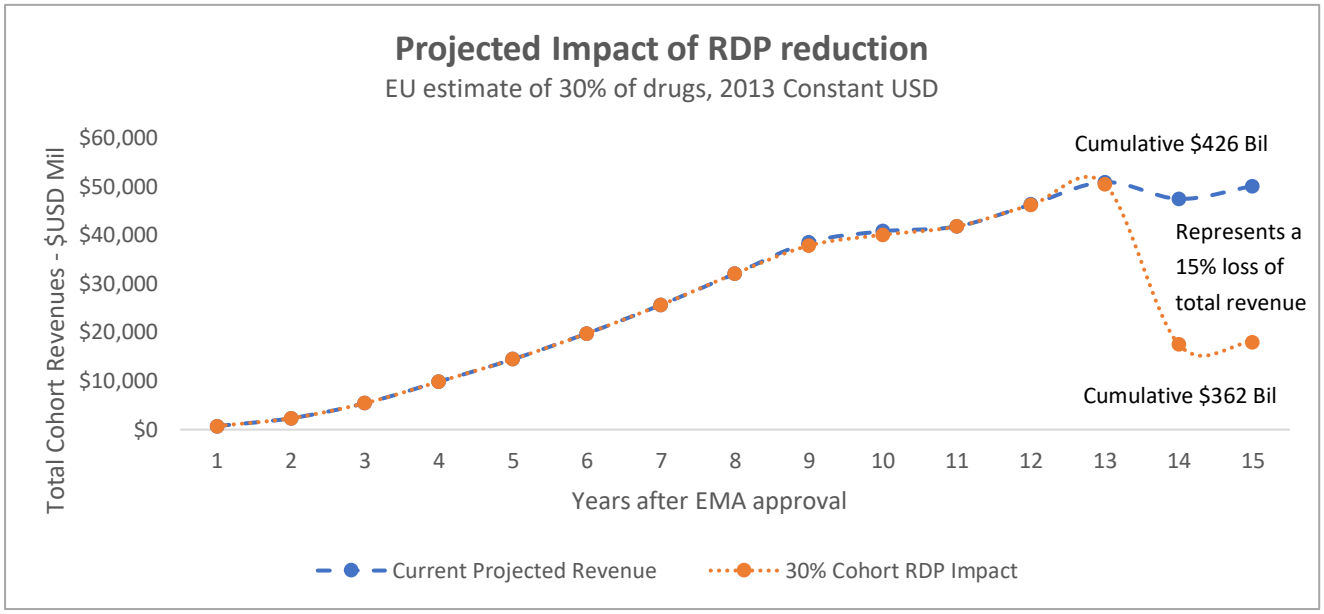

Figure 6 Companies lose 15% of total EU revenues due to a 2-year reduction in RDP; simulated cohort of 8 drugs selected at random based upon the EU's assessment of breath of impact due to lost RDP

When simulating the EU's overall finding of the impact of RDP, we see a 15% drop in total EU revenue (measured in constant 2013 USD). In real terms, this represents a decline in revenues from $426 billion before the two-year loss of RDP, to $362 billion afterwards. Assuming the EU's assessments are correct, cuts of revenues which are this substantial will have a demonstrably negative impact upon both innovators and drug developers.

Measuring the impact of clawbacks (i.e., 'price controls') on marketed EU therapies

According to the U.S. Trade Representative report in 2022, "U.S. pharmaceutical stakeholders have expressed concerns regarding several EU Member State policies affecting market access for pharmaceutical products, including non-transparent procedures and a lack of meaningful stakeholder input into policies related to pricing and reimbursement, such as therapeutic reference pricing and price controls."[14]

Increasingly, many EU governments have put restrictions on the annual budgets of biopharmaceutical products, limiting increases in spending on drugs to the rate of inflation. When those limits are exceeded, the ministry of health of the various member states can demand a 'clawback', i.e., an after-sale refund, to compensate for a drug exceeding this revenue cap. This is increasingly being used as a tool to implement 'price controls' on drugs in EU member states.

These policies, while certainly superficially understandable, ignore several key EU trends related to healthcare spending in general. Europe is experiencing radical demographic shifts which are driving up the rate of healthcare utilization and spending.

As populations age, they will consume more expensive healthcare, and Europe's population is aging rapidly. In Germany in 2012, there were already only two workers per pensioner.[15]

As well, these demographic shifts put extreme pressures upon the fewer and fewer workers available to contribute into the social safety net through tax revenues. Increasingly this situation is leading to decisions within member states to put in place price controls, i.e. clawback provisions, to control the spending on medicines.

The emerging problem regarding clawbacks can be seen in Figure 7 which is taken directly from a report published by a commission of inquiry of the French National Senate on 4 July, 2023.[16] The growth in French clawbacks exceeds 900% since 2015. The report highlights that the French government's price control policy had, "traditionally acted as a subsidiary mechanism intended to

'make up for' the possible failure of conventional tools for controlling drug expenditure (price reductions, rebates), it now exceeds its role [as a] regulation tool."[17]

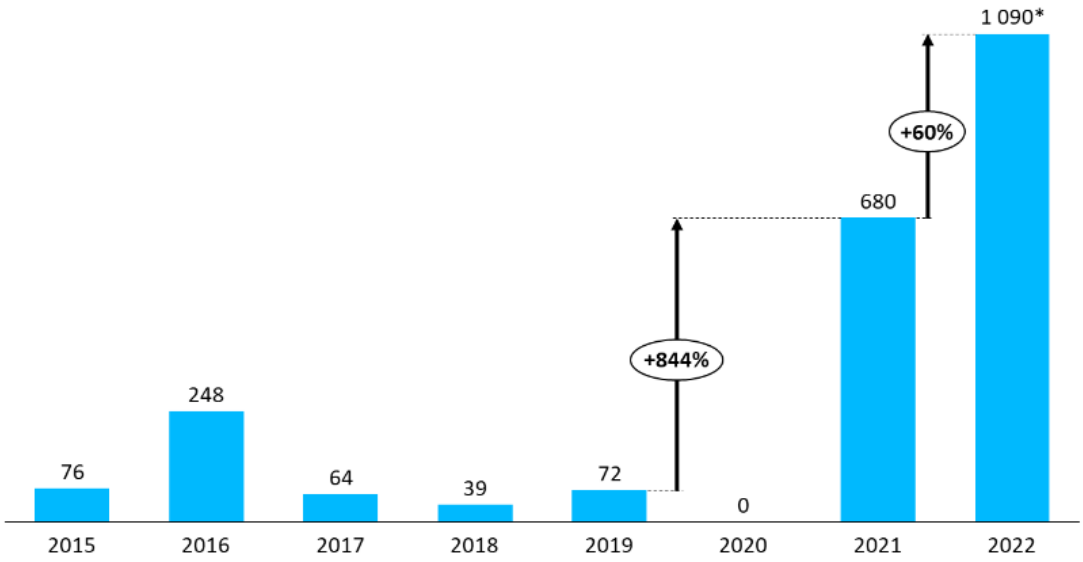

Figure 7 Source: French Senate Commission of Inquiry on the increase of clawbacks, July 2023, Mil EUR

The French Senate's report also illustrates another problem for innovators: as of the report's publication in mid-2023 the clawbacks under discussion were based on 2022 revenues which had not yet been finalized when the report was distributed. This means that, for a company impacted by these clawbacks, planning for future R&D and capital investments is delayed due to the lack of clarity regarding the final impact of these French price controls, as many firms would normally have expected to close their books and set budgets for 2023 far before July of that year.

Turning to the UK (Figure 8), on December 5th, 2018, the UK Government and the Association of the British Pharmaceutical Industry (ABPI) agreed to implement the, "Voluntary scheme for branded medicines pricing and access [VPAS], an agreement . . . getting the best value and most effective medicines into use more quickly."[18] However, in February of 2023, ABPI had highlighted that, "The cap mechanism [VPAS] has led to rocketing revenue clawbacks in the UK, up from around five per cent to 27 per cent in just three years, well beyond any historical or international comparison." As of Q1 of 2023, this clawback under the VPAS agreement represented a 1,245% increase in size from its inception.[19]

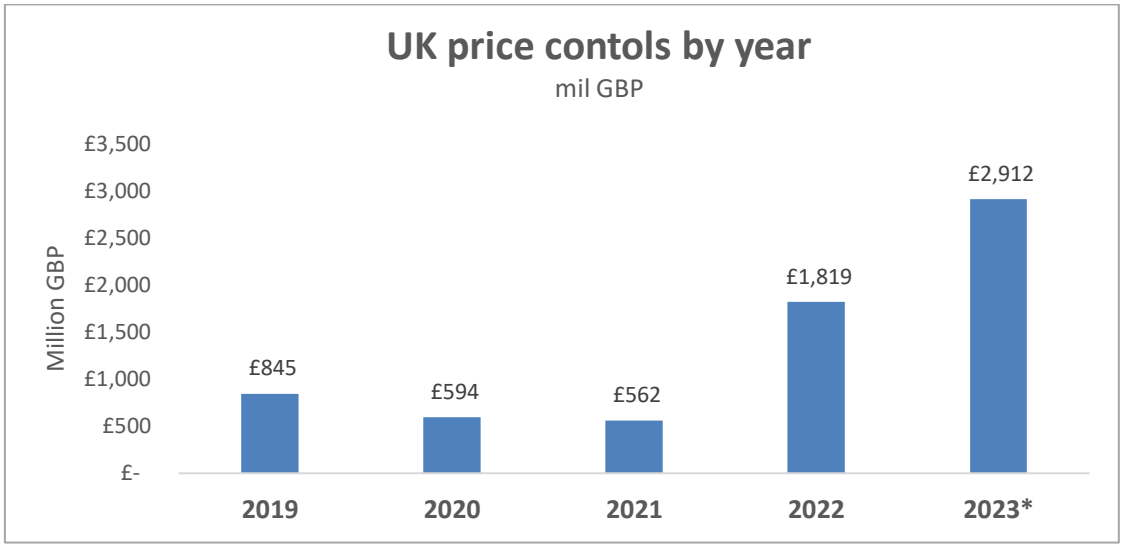

Figure 8 UK clawbacks in 2023 were projected to be nearly 30% of sales. The 2023 impact has been projected upon three quarters of data

Given these huge increases, in November of 2023, Britain's biopharmaceutical industry and the UK government agreed to new and revised clawback terms under the voluntary scheme for branded medicines pricing, access and growth ("VPAG"), which assumes a growth rate of 4%.[20] Given the previous VPAS was designed as a 'fix' to the statutory regime, it remains to be seen if the VPAG will be more successful than VPAS at both maintaining a fair price control whilst not impairing innovative capital.

While variable by market, price controls via clawbacks are increasing in general, taking up a larger percentage of EU net revenue (Figure 9). The problem from an innovator's standpoint is the uncertainty created by regulatory reforms in Europe, both in the member states as well as in Brussels at the European Commission, as these impacts are meaningful.

For example, "At the end of 2021, the members of Farmaindustria made a clawback payment of approx. €331 million. Such payment referred to the financial year 2019 when the agreement was still in force."[21] As of the time of this publication, Spain's industrial drug rebate payments have not been reinstated, but they are under consideration by the government.

Country	PV Revenue Loss 2012 - 2023		Percent Loss	PV of Revenue 2012 - 2023	
	loss per year	total loss		without clawbacks	with clawbacks
France	(€ 18,890,677)	(€ 226,688,123)	3.5%	€ 6,489,136,337	€ 6,262,448,214
Germany	(€ 3,364,781)	(€ 40,377,367)	0.5%	€ 7,797,072,175	€ 7,756,694,808
Italy	(€ 7,461,289)	(€ 89,535,473)	2.5%	€ 3,647,351,362	€ 3,557,815,889
Spain	(€ 9,685,445)	(€ 116,225,335)	4.7%	€ 2,451,578,685	€ 2,335,353,350
UK	(€ 63,863,994)	(€ 766,367,927)	15.0%	€ 5,124,461,559	€ 4,358,093,632
Totals	(€ 103,266,185)	(€ 1,239,194,225)	-4.9%	€ 25,509,600,118	€ 24,270,405,893

Figure 9 Impact of price controls by market, 24 drug cohort. Values in 2023 EUR.

Vital Transformation developed an estimate of the future impact of clawbacks based on data for 6 countries (France, Germany, Italy, Spain, Switzerland and United Kingdom) over 11 years (2012-2022). We find that growth rate in clawbacks currently exceeds the increases in sales by roughly 20% per year in our 24-drug cohort (Figure 10). This means that, by 2033 if they continue unabated, they will exceed 100% of all our cohort's sales.

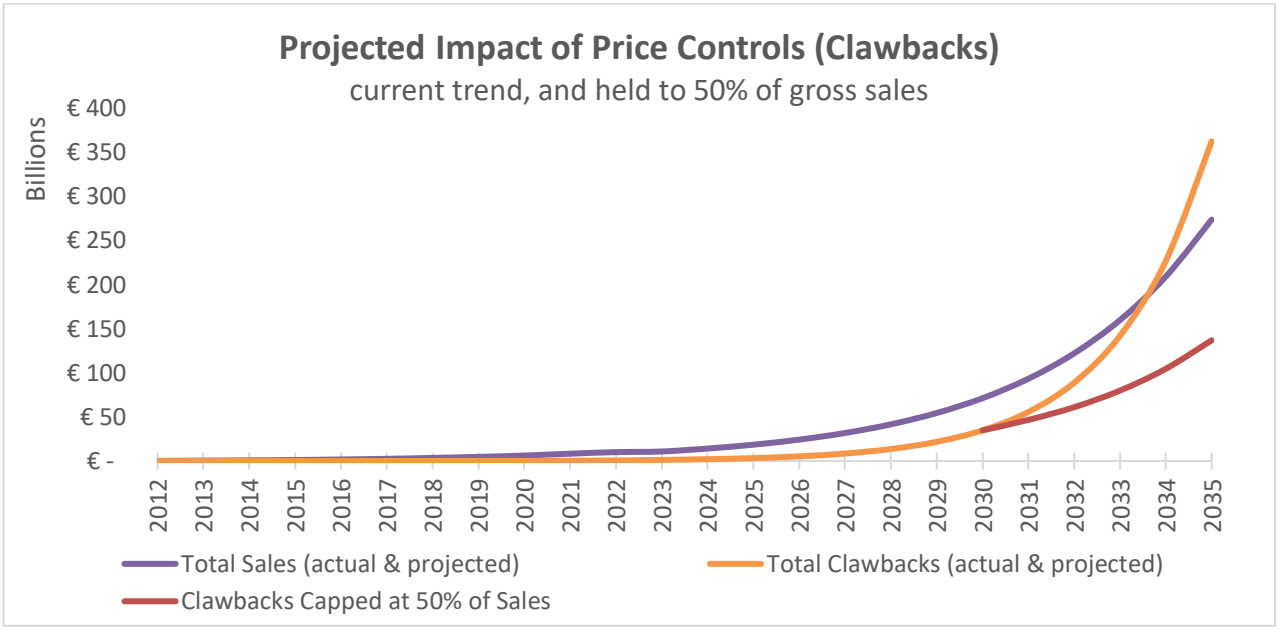

Figure 10 Values in constant 2015 EUR. Projected values starting in 2024 use median annual growth rates: Sales = 27% per year; Clawbacks = 47% per year

Whilst it unlikely that governments will allow price controls to exceed 100% of sales, the current trends are clear. We can model the future impact of all current price controls on our cohort, combining the impacts of clawbacks and RDP, under the current growth rate, and an assumption limiting clawbacks to 50% of projected future revenues. It should also be noted that a restricted clawback at 50% still yields a revenue impact of roughly €100 billion in the EU, these are extremely large rebates that will have a negative impact upon EU investments and drug development.

Measuring the impact of the GPL's RDP incentives

While the proposed General Pharmaceutical Legislation (GPL) reduces by two years the period of available RDP, it also allows companies several opportunities to recapture those periods. Those include:

- +2 years for medicinal products supplied in all EU 27 Member States within a 24-month period specifies that this must be both "continuously supplied" and at a "sufficient quantity" for the life of the extension.
- +6 months year for addressing unmet need defined as there being no medicinal product authorized in the EU for such disease with a high morbidity or mortality and the use of the medicinal product results in a meaningful reduction in disease morbidity.
- +1 year for a new indication providing significant clinical benefit (can only be granted once).
- +6 months for New Active Substances ("NAS") that are being tested in a comparative effectiveness RCT.

Cumulatively then, it is at least theoretically possible for a company to have 12 years of regulatory data protection for a new therapeutic.

However, as many of these 'incentives' require large upfront investments by a company, with no guarantee of success, the question becomes what, on average, is the value of these incentives? Given that many of these incentives are perishable, in that you need to make investments into meeting their criteria early in the market access period, it does present a challenge as they will require making large investments, both in terms of money and time, to meet these objectives.

Again, we see that these 'incentives' add uncertainty and risk in an EU market where innovation is unquestionably in decline.

As the European Commission has stated that its core objectives with its revised pharmaceutical strategy is to create an, "Innovation-friendly environment for research, development, and production of medicines . . . by promoting world-class innovation, governed by stable and consistent rules,"[22] how will these incentives work in practice? For example, if an EU-based company with a novel indication were to bring a product to market, what would be the likely return on its investment in attempting to fulfil the requirements to have a guaranteed two-year extension of RDP by gaining market access in all 27 EU member countries?

VT has calculated the marginal costs and net present value of such an investment, by theoretically expanding our current 24-drug cohort into all EU member states and developing a framework for such an investment. We see that the total annul combined variable and fixed costs would be roughly equal to $10 million USD, per firm, per year (Figure 11).

Country	Market access	Legal	Office	Rental Cost per Sq Meter	Rental Fixed Cost	Variable Cost	Fixed Cost
Austria	$98,111	$98,111	$119,160	$49,283	$381,467	$292,953	$306,451
Belgium	$111,097	$111,097	$159,499	$52,126	$181,651	$348,509	$145,929
Bulgaria	$48,000	$48,000	$25,967	$26,537	$110,570	$119,300	$88,826
Croatia	$37,204	$37,204	$50,204	$27,011	$253,679	$121,805	$203,793
Czechia	$45,807	$45,807	$56,903	$50,230	$163,802	$159,664	$131,590
Denmark	$150,793	$150,793	$160,760	$39,805	$381,467	$403,404	$306,451
Estonia	$55,961	$55,961	$54,499	$35,698	$254,311	$162,372	$204,301
Finland	$126,968	$126,968	$123,527	$75,820	$292,221	$364,145	$234,755
Greece	$87,691	$87,691	$27,738	$51,178	$253,679	$204,290	$203,793
Hungary	$51,030	$51,030	$30,578	$26,442	$150,059	$127,797	$120,550
Ireland	$114,000	$114,000	$105,437	$110,507	$284,323	$356,642	$228,411
Latvia	$23,568	$23,568	$42,912	$31,276	$253,679	$97,465	$203,793
Lithuania	$35,243	$35,243	$41,313	$32,223	$254,311	$115,700	$204,301
Luxembourg	$132,701	$132,701	$159,499	$102,356	$434,383	$423,571	$348,961
Netherlands	$91,200	$91,200	$124,983	$78,189	$268,527	$309,749	$215,721
Poland	$68,840	$68,840	$38,002	$51,652	$159,537	$182,628	$128,164
Portugal	$47,624	$47,624	$-	$51,178	$157,957	$117,632	$126,895
Romania	$23,459	$23,459	$30,169	$49,283	$254,311	$101,520	$204,301
Slovakia	$58,852	$58,852	$40,670	$31,276	$148,322	$152,354	$119,154
Slovenia	$58,247	$58,247	$73,312	$29,380	$292,221	$176,083	$234,755
Sweden	$174,810	$174,810	$117,852	$81,180	$270,581	$440,759	$217,371
					TOTAL	**$4,778,342**	**$5,348,490**

Figure 11 Variable and fixed costs per firm per year to access additional EU 27 member countries, 2022 dollars, total is $10.13 million a year.

Further, we assume these costs would not be short term, as a company with a successful drug will also be engaging in drug development. We estimate that a firm will maintain these investments to support their operations in all EU 27 member states if they want to maximize their opportunity of maintaining market access and ensure a gain of two extra years of RDP.

We currently have 13 firms in our cohort, for a net annual increase of required investments of $131 million. Our calculations assume an NPV (discount rate on capital) of 11%, which is an industry standard for drug development.

Result 1: NPV for our current 24 drug cohort of gaining two years of extra RDP

Total Entry Cost of 13 firms, 27 Countries, NPV ($US Million, 2013 USD)	-$694.70
NPV Gain from 10 years of RDP	$289.43
Net NPV Gain (Loss)	**$ (405.27)**
Net Gain (Loss) per Firm	**$ (31.17)**

As we only have two drugs impacted by losses of RDP in our analysis cohort, the -$405 million loss in NPV does not justify the expense of investing to gain market access in all 27 EU member states to regain two lost years of RDP. However, the GPL also makes provisions allowing for up to 12 years of RDP, assuming a company successfully meets several criteria. Does this incentive justify any investment given an ROI analysis?

Result 2: NPV for our current 24 drug cohort of gaining an extra four years of RDP for 12 years total

Total Entry Cost for 13 firms, 27 countries (NPV) ($US Million, 2013 USD)	-$ 694.70
NPV Gain from 12 years of RDP	-$ 545,00
Net NPV Gain (Loss)	**$ (1,239.70)**
Net Gain (Loss) per Firm	**$ (95.36)**

In our calculation of the impact on the NPV of all the companies in our cohort obtaining 12 years of RDP, we see that the NPV becomes increasingly negative with losses now totalling -$1.2 billion. We've been conservative in this calculation and have assumed a total of 12 years of RDP will not

require further investments beyond the annual costs that are already being spent to access all 27 member states within 24 months, which is an unlikely scenario.

The cost of running comparative outcomes trials, for example, is both expensive and time consuming, as these are longitudinal studies based upon outcomes. According to biotechnology entrepreneur Steve Potts, "we budget $200,000 per patient, that's basically five patients per $1 million . . .that's what it takes to adequately have a patient enrolled [in clinical trials]."[23]

The above NPV calculating twelve years of RDP assumes none of the extra costs to conduct the clinical trials required to obtain these incentives. Adding these to our analysis would make the results significantly worse. This result represents a very "best-case" scenario.

Result 3: NPV for our current 24 drug cohort with RDP impacting our 8 drug EU random sample

The EU has stated that its internal review has determined that roughly 30% of all approved patented therapies will be impacted by RDP reductions under the GPL. Using our previous random sample of 8 drugs taken from our cohort to determine the revenue impacts due to reduced RDP, we can model a theoretical NPV of those 5 manufacturers investing in market access in all 27 member states to increase their RDP from 8 to 10 years.

Total Entry Cost for 13 firms, 27 countries (NPV) ($US Million, 2013 USD)	-$ 694.70
NPV Gain from 8 drug EU sample gaining 10 years of RDP	$ 916.28
Net NPV Gain (Loss)	**$ 221.58**
Net Gain (Loss) per Firm	**$ 17.04**

Interestingly in this theoretical scenario, the NPV is modestly positive at $17 million per firm in our eight-drug sample. However, more generally, it is important to consider the impact of this NPV model on a drug-by-drug basis across our entire cohort (Figure 12).

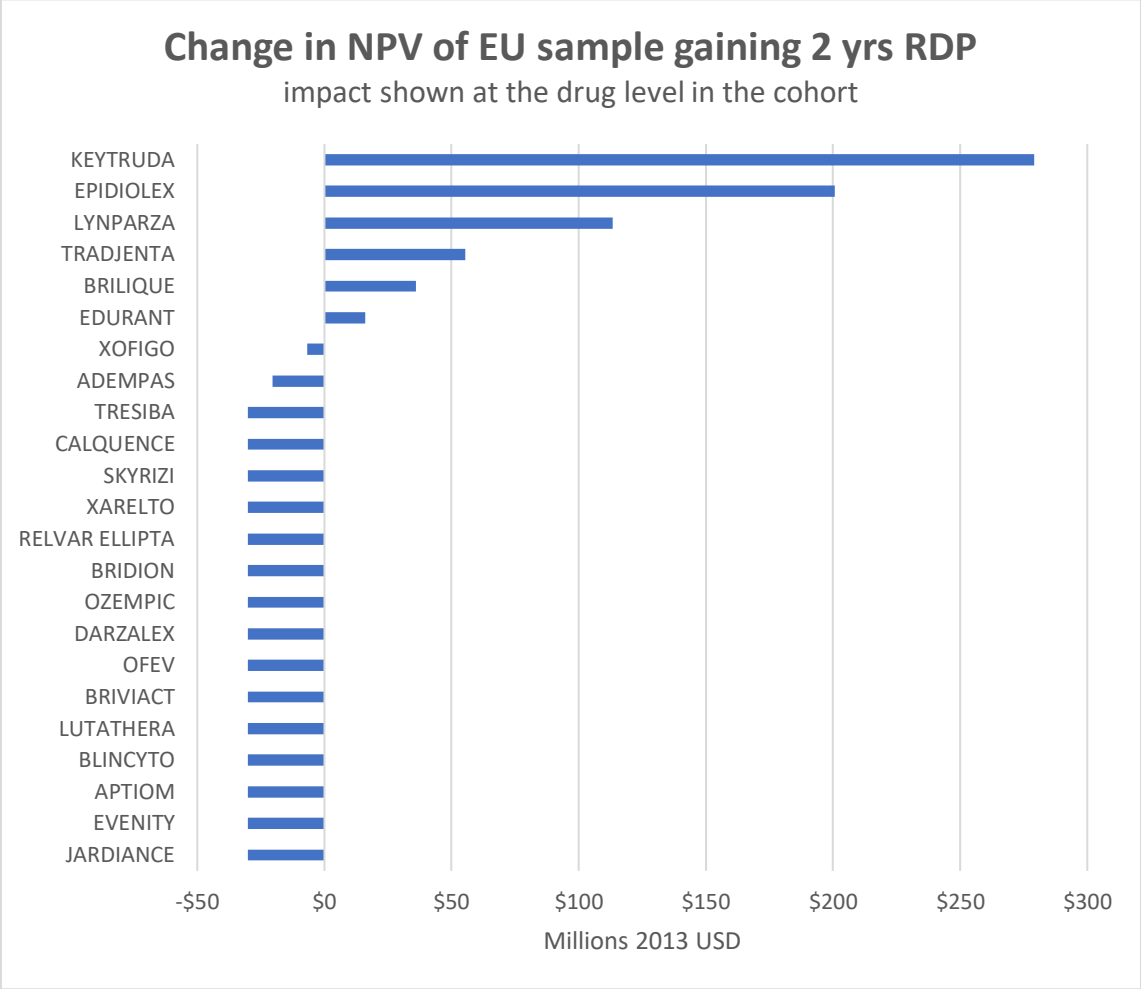

Figure 12 NPV model of EU 30% projected RDP impact for entire cohort shown drug by drug

As Keytruda, and to a lesser extent Tradjenta, and Brilique, were included as part of our random sample of drugs to test the EU's hypothesis that 30% of all therapies will be impacted by RDP reductions, the extra billions of dollars a year in aggregate gross sales for those drugs swamps any costs that are incurred by the rest of our cohort; those losses are 'hidden' when the cohort's impacts are expressed as an average NPV. One sees that only 6 of our 24 therapies have a positive NPV when the impacts are calculated based upon the individual drug and firm level, and the NPV is negative for 75% of our therapies.

From a strategic standpoint, the challenge for a drug developer is that the infrastructure and investments to support these incentives needs to be in place before a drug is approved by the EMA.

This will be seen as an added cost to the investment, increasing the risks upon an already uncertain ROI which only occurs at the END of the payback period, when the revenues are the most discounted.

Keytruda, while a blockbuster now, only produced $55 million and $544 million of global revenues in its first two years on the market, the period when Merck Sharp & Dohme would have been required to secure market access in all EU member states. It is highly unlikely that at the time of its launch that spending an extra $10.1 million a year to obtain a theoretical benefit of extended RDP, assuming it's even possible or beneficial to gain market access in all EU 27 member states, would seem like a prudent use of precious cashflows.

This would even more true for a small company with a novel therapy. Would an emerging biotechnology firm spending 44% of its cashflow on R&D with an EU conditional approval for an orphan therapy have the resources and regulatory know how to staff and mount an advocacy campaign in 27 EU member states and gain market access within 24 months? This prospect seems highly unlikely.

In our analysis, the only positive NPVs for utilizing these incentives is found in blockbuster drugs based upon a simulation of the European Commission's own internal assessment stating that roughly 30% of drugs will be impacted by RDP reductions. This assertion does not conform to what is seen in our own live dataset of therapies based upon audited sales in the EU, whereby only 8% are impacted by RDP reductions.

Further, and perhaps more importantly, as these incentives would require significant financial and operational resource allocation, with speculative sales at the time of launch, we're far less than certain how practical they are both at improving access to patients in all 27 EU member states, nor in arresting the continued marked decline in global EU biopharma competitiveness.

Additionally, many countries outside of the EU, such as Australia, New Zealand, Canada, etc., will benchmark or 'reference' the prices applied in other countries, particularly countries in the EU, for their own internal price for a medicine at launch. Given the implementation of collective bargaining

partnerships in the EU such as the Beneluxa initiative,[24] the fact that many of the current EU 27 are not always receiving access to medicines is also a function of the global market. Obtaining market access in a Central and Eastern Europe (CEE) country to meet the 27-member state goal may require the innovator company to offer prices substantially lower than economically feasible, or at least far below current market rates.

This will not only increase the cost of market access due to the need to invest in meeting the 'incentives' of the GPL, but also puts prices outside of the EU at risk for those countries which benchmark to EU prices. In this scenario, companies would see a downward spiral of pricing internationally. In this sense, given the uncertain and questionable NPV in meeting the criteria for the GPL's incentives, it's highly unlikely that they will be utilized, nor will they promote biopharmaceutical innovation in the EU.

EU investments and start-ups in biotechnology and pharmaceuticals, 2011 – 2023

One of the justifications for the launch of the GPL was outlined in the European Commission's Q&A document released on the 16th of March 2023. It states,

> "The EU has quickly reacted to the disruptions caused by the COVID-19 pandemic and Russia's war of aggression against Ukraine with a common coordinated response, demonstrating that our common strength is greater than the sum of all Member States' efforts . . . The long-term view is articulated around nine mutually reinforcing drivers [including] research and innovation."[25]

The desire for a cogent centralised response to COVID-19 which includes EU research and innovation is also articulated in the European Parliament's ITRE Committee report published in March of 2021. The report states,

> "In order to support the strategy, the new €5.1 billion EU4Health programme was agreed upon in December 2020. It aims at ensuring the availability and accessibility of medicines,

including the COVID-19 vaccine, by encouraging and financially supporting European pharmaceutical research."[26]

Given the above statements, and the €5.1 billion EU4Health programme funding allocated to the sector, we should be able to ascertain changes in market behaviour, both before and after COVID-19, within the EU biopharmaceutical sector. One assumes that the European institutions are fully aware of the need to respond to the impacts of COVID-19 on EU biopharmaceutical innovation. Obviously, if this is the declared motivation for the need for regulatory changes and the implementation of the GPL for the biopharmaceutical sector, the data must surely be conclusive.

From the Biomedtracker database, VT extracted a dataset of 527 EU biopharmaceutical companies created in the EU from 2011 – 2023.[27] The results are intriguing as they show that while the EU does see a large drop in biopharmaceutical company creation over this period, the largest decrease occurs in 2018, two years before the COVID-19 pandemic swept through the EU (Figure 13).

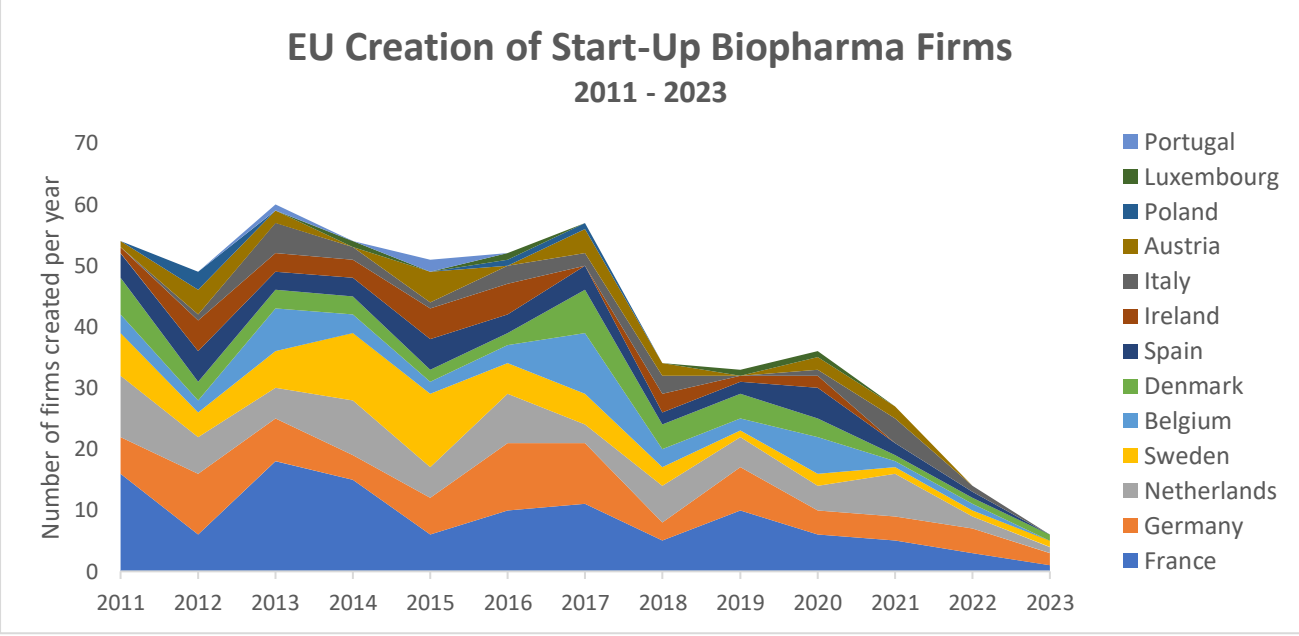

Figure 13 Source - Biomedtracker

Prior to passage of the U.S. Tax Cuts and Jobs Act of 2017, the U.S. corporation tax rate was 35 percent. At that time, Europe had the lowest regional average corporate tax rate globally, at 18.35 percent.[28] Under U.S. corporate tax law, any company registering profits abroad prior to the

passage of the Tax Cuts and Jobs Act would be required to pay the difference between the tax rates of the two countries on those profits to be able to repatriate those funds held in treasury abroad back to the U.S. As this 'tax penalty' for repatriating profits back to the U.S. from the EU was roughly 18%, it was beneficial for those funds to be held abroad, as there was no penalty for making investments or using those funds from within the EU.

According to a March 2017 report by the Washington DC-based Institute on Taxation and Economic Policy, U.S. companies before the Tax Cuts and Jobs Act held $2.6 trillion in non-repatriated profits abroad.[29] Their report further shows that a substantial portion of these foreign held treasury funds were in the pharmaceutical sector (Figure 14).

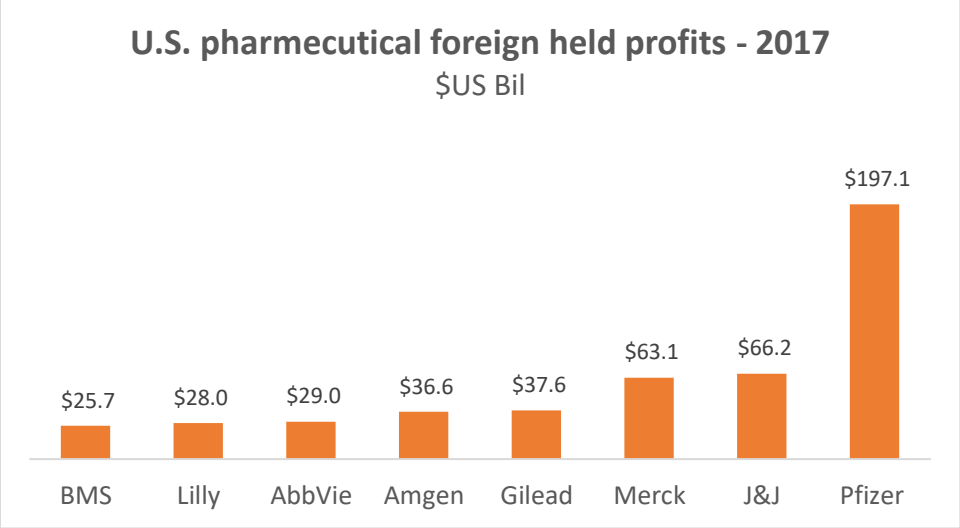

Figure 14 Source - Institute on Taxation and Economic Policy

With the passage of the Tax Cuts and Jobs Act, on January 1st, 2018, U.S. corporate tax rates fell to 22%, near the OECD average, and the 'penalty' for repatriating U.S. retained earnings back to an American corporate entity was substantially reduced. According to the U.S. Federal Reserve, "U.S. firms repatriated $777 billion in 2018, roughly 78 percent of the estimated stock as of end-2017 of offshore cash holdings."[30]

When investigating investments made into EU biopharmaceutical sector under $10 billion in value (i.e., not one-off blockbuster acquisitions) we see a marked change in EU deal making behaviour

after 2018. According to data obtained from pitchbook (Figure 15), there is a pronounced drop of 40%, from $34 billion to $20 billion of investments which occur between 2018 and 2019, roughly correlated to the changes in 2018 U.S. tax policy.

What this demonstrates axiomatically is that prior to the 2018 U.S. corporate tax changes firms were using their funds held abroad to make strategic deals, partnership and acquisitions within the EU, as there was an enormous penalty for bringing those funds back to their U.S. corporate headquarters. In 2018, those tax incentives disappeared, and with it there was a substantial reduction in capital supporting the EU biopharmaceutical sector .[31]

Perhaps the EU's policy prescriptions for the biopharmaceutical sector 'in reaction' to COVID-19 are misplaced, at least rhetorically? When researching cause and effect, the cause generally occurs before the effect, not after. Instead, the evidence demonstrates that, due to challenges in the global competition environment, including US corporate tax changes, Europe's life sciences decline began well before COVID-19.

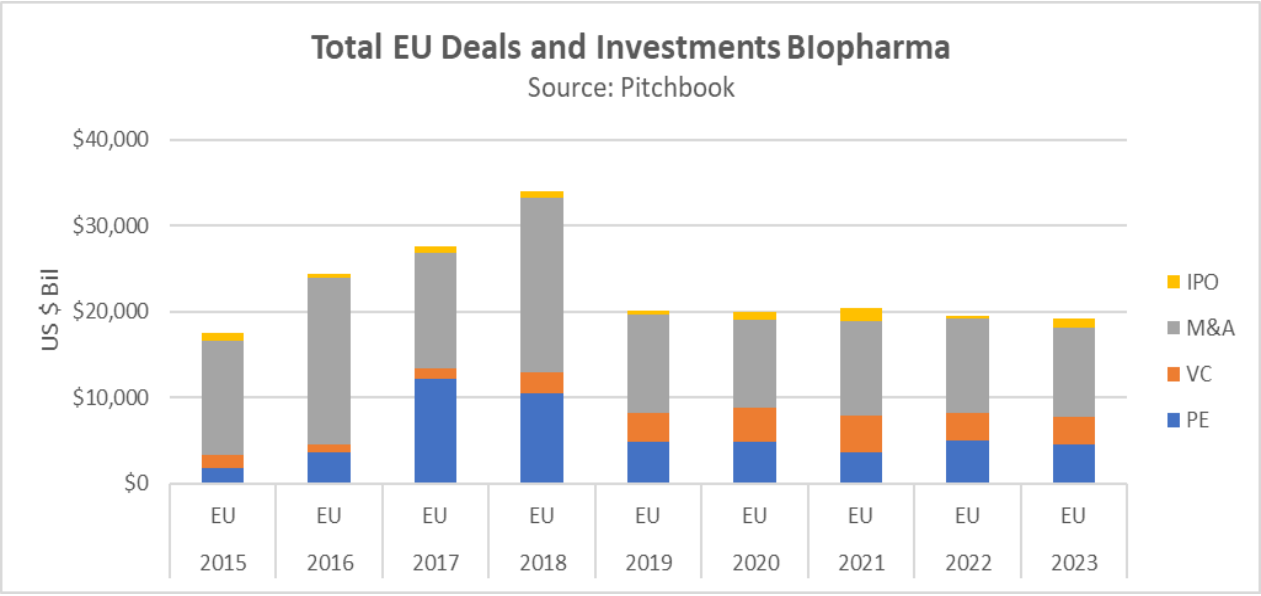

Figure 15 Source - Pitchbook, total EU biopharma deals < $10 billion in size

Whilst EU investments fell markedly after the passage of the U.S. corporate tax changes, we see a large increase in U.S. dealmaking, nearly doubling through 2021 (Figure 16). We do see a decline in

2022, but we attribute this not to COVID-19, but instead to the introduction of the Inflation Reduction Act (IRA) legislation in June of 2021, which was eventually passed in August of 2022.[†]

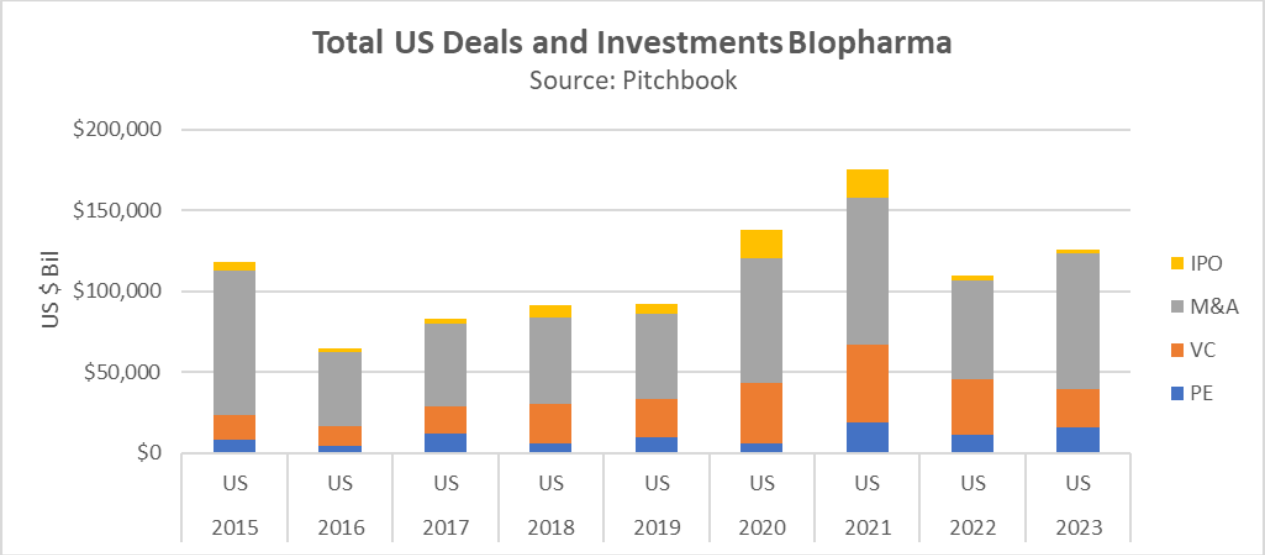

Figure 16 Pitchbook, total US biopharmaceutical sector deals < $10 billion in size

The current relative sizes and scope of the EU and U.S. biopharmaceutical markets should be kept in context (Figure 17). Any policy prescriptions in the EU which harm its global competitiveness will only add to the disequilibrium that is currently observed. If Europe is serious about it continuing, "to offer an attractive and innovation-friendly environment" it must make policy recommendations that improve the competitive landscape, as the sector, since 2018, has been in marked decline. This decline appears to have nothing whatsoever to do with the impact of the COVID-19 pandemic.

[†]VT is currently engaged in an analysis of the Inflation Reduction Act's impact on global biopharma innovation to be released in June of 2024 which is outside the scope of this research paper on the GPL.

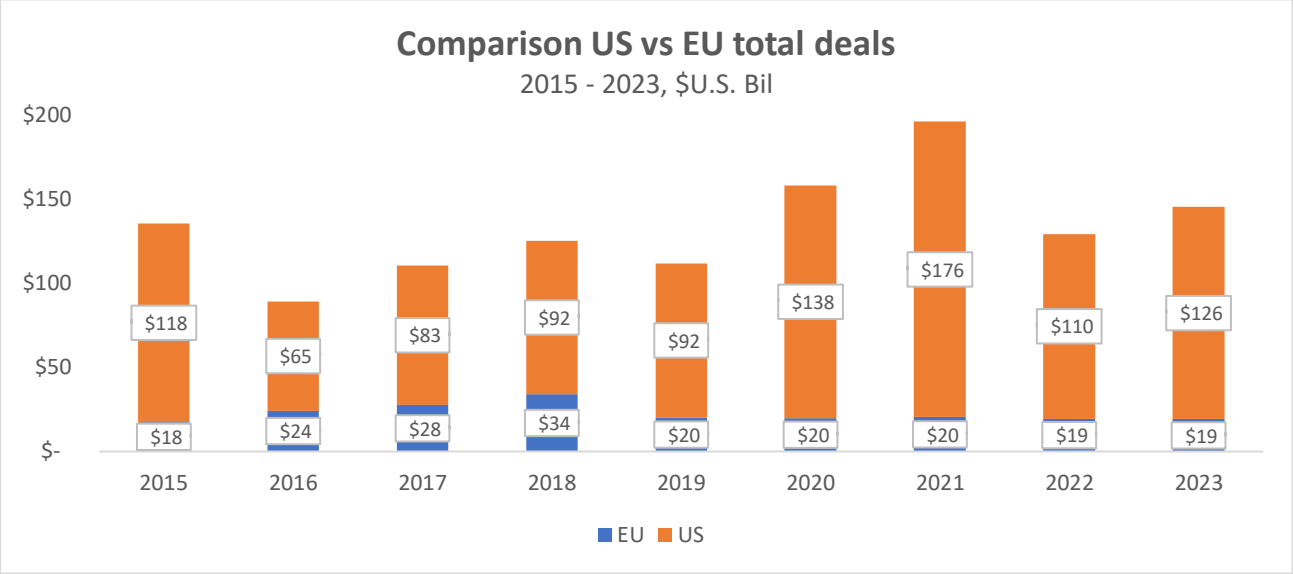

Figure 17 Pitchbook, total US & EU biopharma deals < $10 billion in size

The investment beta 'β' – predicting responses to regulatory changes and market risks

The fact that the data demonstrates this decline in European competitiveness derives from pre-COVID environmental policy gaps between global markets underscores the importance of ensuring that the changes in the policy environment for innovative biopharmaceuticals (e.g., changes to the GPL and continuing price control measures through clawback mechanisms) do not inadvertently accelerate these negative trends.

One of the challenges prognosticating future events is finding a quantifiable and measurable way to determine how markets and people will react to an event which has not yet occurred. Previous work in this study has harnessed actual audited data. When predicting how investors and innovators will respond to incentives and uncertainties, we will use a measure of behaviour called a market Beta, written β, to anticipate the impact of the GPL.

A market β measures the volatility of the returns of an investment asset, or a portfolio of investment assets like an index fund, relative to a 'global' market benchmark such as the S&P 500

listing of the top 500 tradable companies. β is a standard metric; it is regularly used to calculate the expected return on an asset and to determine whether an asset is correctly valued (priced).

We find the beta 'β' by calculating the covariance between the return (r_a) of a stock or index and the return (r_b) of another stock or index divided by the variance of the other index over a period of several years.

$$\beta = \frac{\mathrm{Cov}(r_a, r_b)}{Var(r_b)}$$

This formula describes how volatility between markets increases risks, which then require a higher rate of return. If uncertainties in one market are increased (say, by attacking data protection, or through major changes in international tax policy), β will quantify the difference in returns between alternative investment opportunities. Greater uncertainty regarding an asset's future ROI implies a lower value of its β when compared to other investible opportunities, such as the U.S. Nasdaq biotech index, or other assets in general.

Our hypothesis is that β should be an accurate predictor of market behaviour and risk levels between the EU biotech market, US biotech market, and the global Standard and Poor's 500 index. In this case, a prediction model using β could be used to accurately predict future changes to RPD as a market risk and provide insights as to how investors will respond.

Euronext, Stockholm, and the Nasdaq biotech indices since 2011

VT has calculated the daily β coefficient of returns since January 3rd, 2011, comparing the Euronext, Stockholm and Nasdaq biotech indices to the S&P 500. This represents 12,976 datapoints.

Whilst there is always variation in their number and types of biotechnology firms, the Euronext and Stockholm indexes are comprised of emerging and start up biotech companies based within the EU

27. We estimate that these indexes consist of roughly 60% of all the indigenous publicly traded biotech startups in the EU and are a representative sample of European biotech activity.[‡]

The historical β of our various indices shows that the Nasdaq biotech index has nearly equalled the returns of the S&P 500 since 2011 (Figure 18). We also see that the Euronext has only returned 55% of the S&P and the Stockholm index has returned even less.

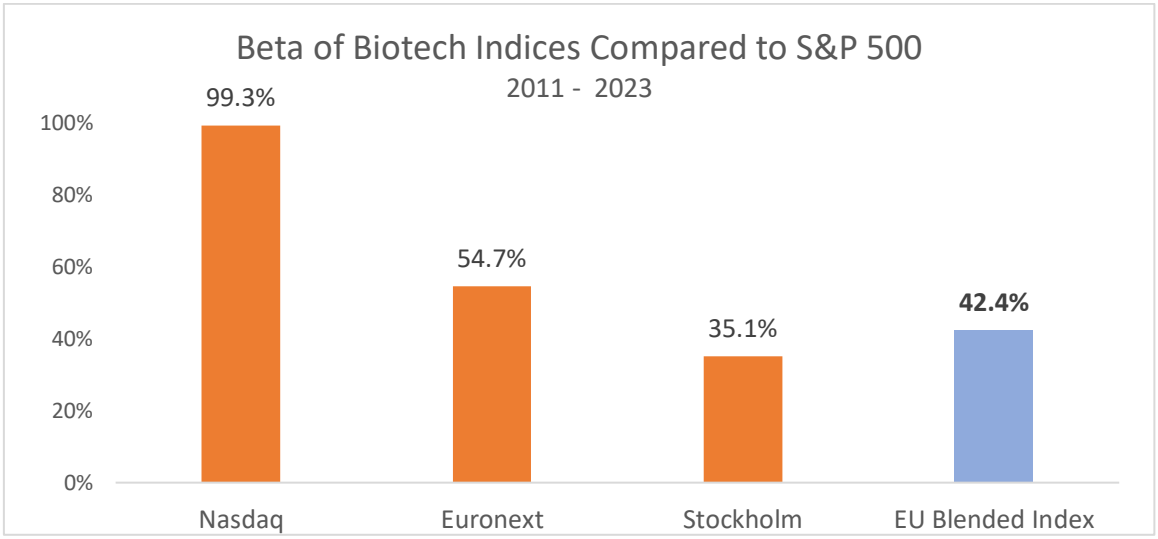

Figure 18 Nasdaq, Euronext, and Stockholm biotech indices, as well as VT's blended EU beta index.

To better test the performance of the European market through a prediction model, VT has constructed a mathematically weighted, 'blended β index' of both the Euronext and Stockholm markets. We assume that investors are logical, and we will test this weighted β in its ability to capture changes in the EU biotech market.

[‡] The Danish OMX biotech index is not included as the recent performance of Novo Nordisk would impart a significant statical skew into our analysis. Novo Nordisk's current market capitalisation exceeds the entire GDP of Denmark, and it is atypical of EU biotech in general.

Our β prediction model of the impact of the GPL on EU biotech

Comparing our blended EU β index as a model to the number of companies created provides both a highly robust and accurate prediction of EU biotech firm creation from the period of 2015 – 2023 (Figure 19). Our model answers 2/3rd of the variation in actual EU biotechnology firm creation with high statistical significance ($P \leq 0.0005$).

Of note is the large drop in the value of β in 2018. This correlates to both the previous drop in biotechnology firm creation that was observed in our data, and to U.S. corporate tax cuts which were also implemented in 2018. What is also striking is that the precipitous drop in EU biotechnology firm creation was not during COVID-19 but instead began in 2017, which mirrors a large drop in the β in 2018.

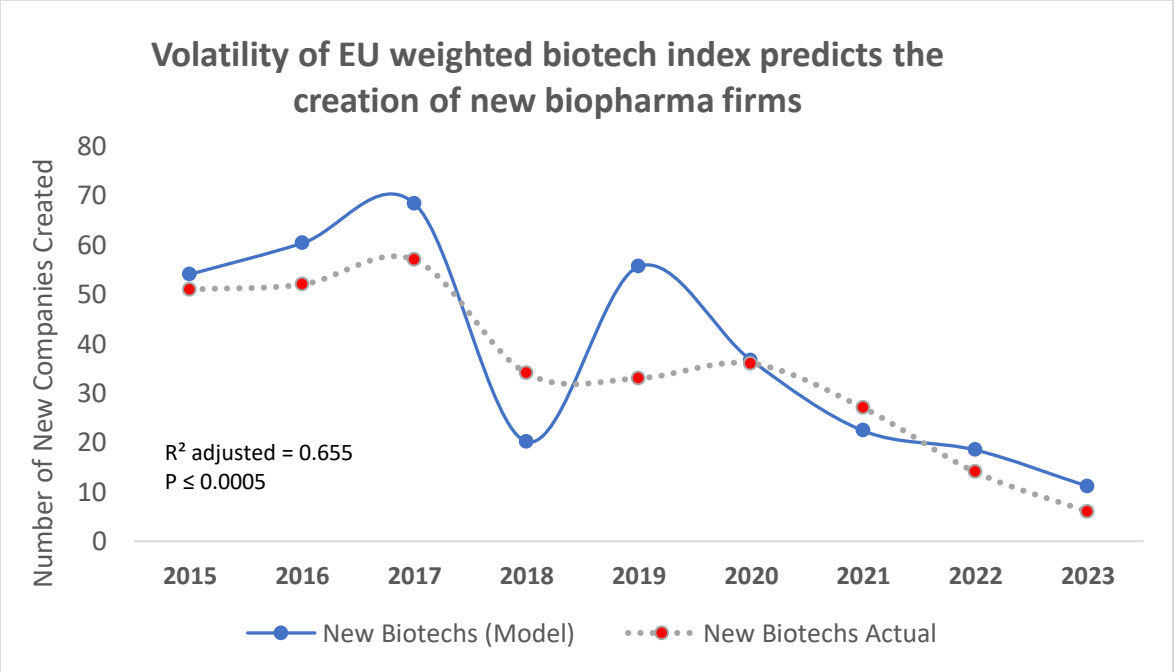

Figure 19 Source: Biomedtracker

Comparing our blended EU β index as a model for the aggregate total amount invested into EU biotech also provides a highly robust and accurate prediction of EU biotech firm investments from the period of 2015 – 2023 (Figure 20). Our investment model captures 2/3rd of the variation in

actual cash and deals invested into EU biopharmaceutical sector with high statistical significance (P ≤ 0.0049). In our deals analysis, EU investments react with statistical significance to β with a one-year delay, so these 'lag' effects have been incorporated into our modelling and visual output.

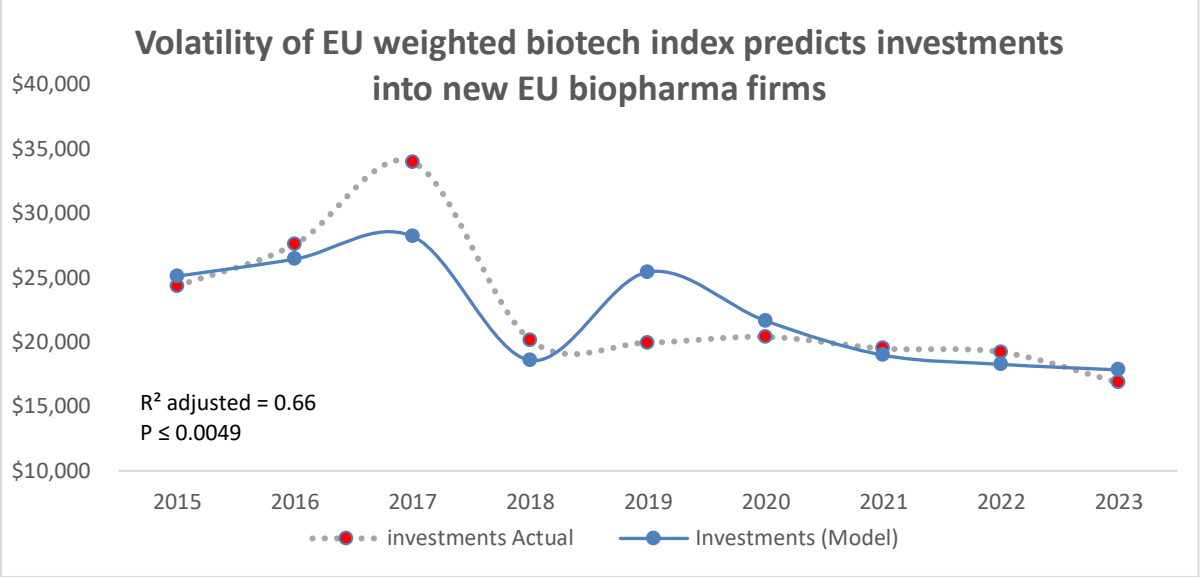

Figure 20 Source: Pitchbook, EU deals < $10 billion. For analysis, the impact of beta on investments is lagged by one year and accounted for in our regression model. This chart shows actual investments advanced by one year to visually indicate this timing of impacts.

Given our model is validated at predicting the EU biotech market, we can now alter the level of β to predict how investors and innovators will respond to the implied changes in risk. Specifically, we use reductions in β as a proxy measure the potential impacts on EU biotechnology sector investments arising from proposed changes to RDP as recommended in the GPL.

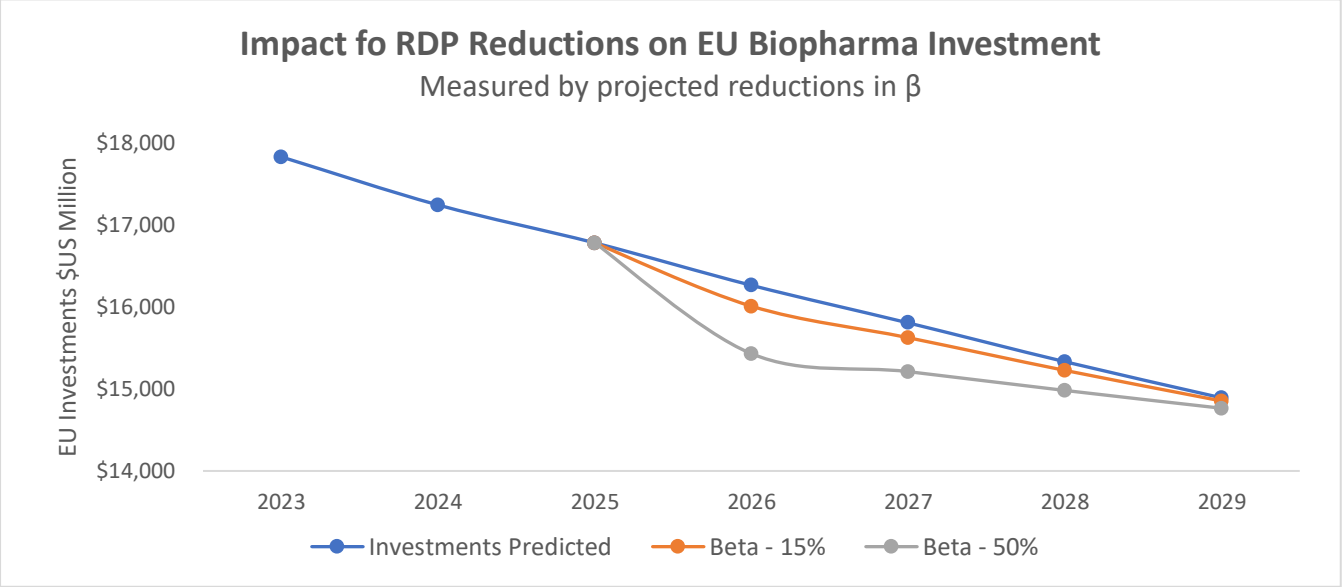

Figure 21 Projected losses of EU investments due to RDP changes

We've modelled the proposed changes in RDP on the investment ecosystem assuming two scenarios (Figure 21). Based upon the EU Commission's own assessment of how >30% of companies will be impacted by reduced RDP, and based upon own previous calculations showing a real 15% revenue reduction across our cohort, we translate this impact into a 15% decrease in β. As well, a more marked increase of investor risk as seen in 2018 with changes to U.S. corporate tax rates can also be modelled, equating to roughly a 50% decrease in β.

The challenge for regulators and innovators is evident in the model; the lack of a return on investment in the EU relative to the U.S. and other global markets is creating a scenario where there is little scope for any relative increase in risk and lowering of biopharmaceutical sector investment returns given the current trends in Europe. The declines in the market projection 'catch up' to the modelled decline in β volatility as those declines are acute.

In 2018, Europe had $34 billion (€31.5) in deals in our dataset that were smaller than $10 billion in size; deals of that scope target both small emerging innovative biopharmaceutical firms, up through midsize innovative biopharmaceutical firms. In all modelled β scenarios, we see that total halving to roughly $15 billion in the current EU economic and regulatory climate.

Any regulatory change which impacts investor certainty in the EU, such as changes to regulatory data protection, will be seen negatively in an already declining EU biopharmaceutical sector investment market. This will put pressure on the measure of β when compared to other investment opportunities globally.

Any decision that requires a substantial outlay of capital with a limited prospect for a return while also increasing risks, like the incentives contained with the GPL, will be seen negatively by innovators and investors.

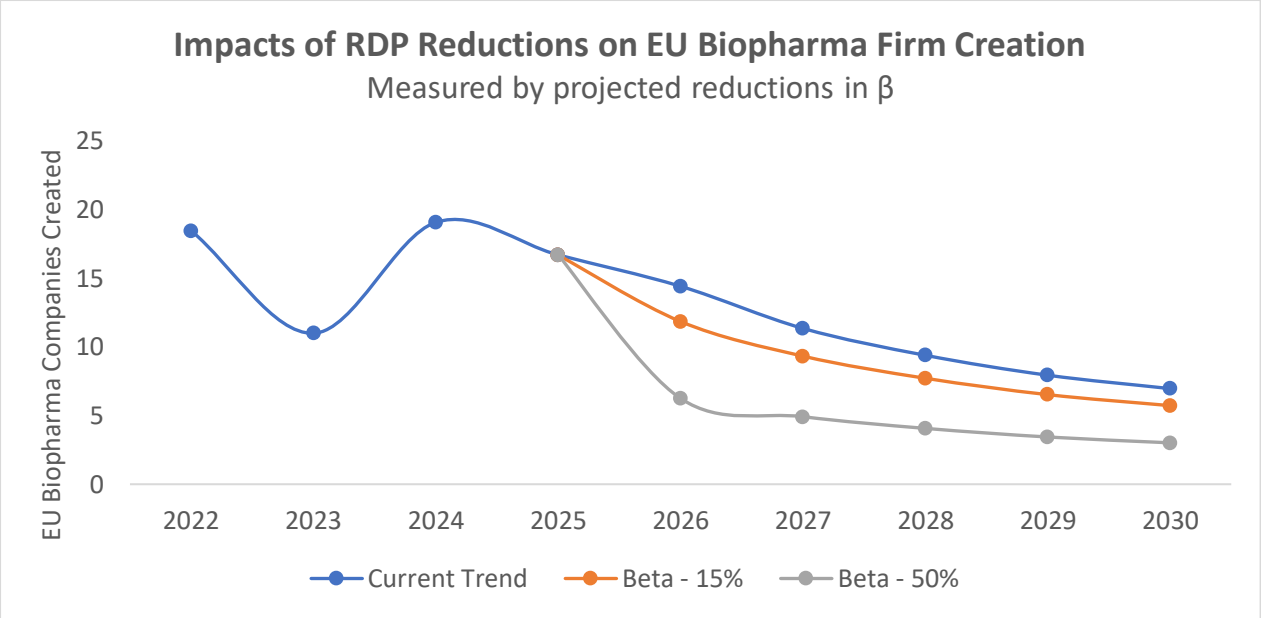

Figure 22 Source: Biomedtracker

As for our β projection for EU biopharmaceutical firm creation, Europe is currently in an extremely unfavourable trend (Figure 22). Our model based upon Biomedtracker data only projected 11 EU biopharmaceutical startup firms in 2023. Suspecting we may have a data problem, we consulted Pitchbook which is known to be the 'best-in-class' dataset for company startups and financial information. Our Pitchbook search yielded a result of only 13 EU biopharmaceutical startup firms in 2023, which is consistent with the predictions of our β model.

For context, our database shows that the EU created 60 Biopharmaceutical startup firms as recently as 2017. Thusly, 2023's total of only 13 companies founded represents a 78% decrease in EU

startup firms over 6 years. Again, if Europe is serious about promoting its innovative biopharmaceutical sector, increasing investor risk by cutting any type of data protection, be it RDP, SPC, or otherwise, hardly seems to be an effective way to arrest the rapidly declining EU biopharmaceutical sector. If investors interpret the GPL to mean higher risk, our model predicts between 3 to 7 EU biopharmaceutical startup firms in 2030.

Conclusions

The challenge for investors and drug developers regarding the potential risk created by a two-year loss of RDP is that there is never 100% certainty that patent protection alone will satisfy the length of time to develop a drug, and there is no way to know if a drug will eventually be impacted by legislative changes more than a decade into the future. Altering data protections will be a strong market signal that investments bear higher risk due to future regulatory changes, and investors in early-stage drug development will alter their behaviour, including exiting the market entirely.

The negative trends in European life sciences indicators dating back to 2018, combined with the continuing downward pressure on EU drug revenues appears to have had a demonstrably negative impact on EU biopharma competitiveness, and increasing market uncertainty with changes to RDP will compound the negative impact in the EU biopharmaceutical ecosystem.

From our cohort of 24 EU invented drugs, we find that two will be directly impacted by 24 months of lost regulatory data protection (RDP), with a total financial impact of -€1.2 billion Euros ($1.3 billion USD); however, the European Commission has estimated that over 30% of all current EMA approved therapies will see revenues impacted by 2 fewer years of RDP - we find a 15% drop (-$64 billion) in total EU revenue in our 24 drug cohort with this assumption, measured in constant 2013 $USD.

The growth rate of clawbacks in member states currently exceeds the growth rate of annual sales in our cohort by roughly 20% per year; assuming no changes in member state policies, clawbacks will exceed our 24-drug cohort's total revenues by the year 2033. We assume that regulators will step away from the cliff of ever-increasing clawbacks, but the pattern in France and the UK, with historical clawback increases approaching 1000%, does not lend one confidence that cooler heads will prevail.

We find that the current EU incentives to extend RDP after a reduction to 8 years (6+2) from 10 will have little positive impact on the EU biopharmaceutical ecosystem. For a firm to seek market access in all 27 EU member states to "reclaim" two-years of RDP, our NPV calculations are nearly

universally negative, and bring into sharp relief the question whether any innovator, particularly a small innovative biotechnology firm that needs to dedicate 44% of its cashflow to R&D, will ever have the desire to put its vitally needed capital at risk to exercise such an 'incentive'.

From a strategic standpoint, the challenge for a drug developer is that the infrastructure and investment to support these incentives needs to be in place before a drug is approved by the EMA. This adds to the cost of the investment, increasing the risks to an already uncertain ROI which only occurs at the END of the payback period, when the revenues are the most discounted.

Finally, the EU has seen a devastating exodus of investment capital from the biopharmaceutical sector, not due to COVID-19, but far more likely due to the unintended secondary impacts caused by the U.S. Tax Cuts and Jobs Act of 2017, which manifested themselves fully in 2019 well before the impacts of the pandemic were felt. These enormous reductions in risk capital are reflected in a precipitous drop in EU biopharmaceutical startup firms, which have virtually come to a standstill in the last 24 months.

Whilst the stated motivations for the General Pharmaceutical Legislation are laudable, and certainly many of its included regulatory provisions to accelerate EMA's approval of new therapies are welcome, the reality is that a faster regulatory approval process will simply speed a drug's arrival to a lack of sales revenue sooner. Europe's biopharmaceutical ecosystem is in serious and rapid decline, and attacks on regulatory data protection, along with increasingly severe clawback policies, despite costly and ineffective measures masked as 'incentives,' will not solve this situation.

Europe must dedicate itself to a vibrant biopharmaceutical ecosystem and maintain its current regulatory data protections. If not, the analysis and data in this report is unequivocal in its findings that the EU biopharmaceutical sector will exacerbate its current rate of decline, creating opportunity for investors to move capital outside of the EU, to markets with more favourable regulatory data protections, such as the U.S. and/or to emerging markets.

Appendix:

Vital Transformation, a real-world evidence, international health economics, and healthcare strategy consultancy, was asked to conduct an analysis of the proposed EU General Pharmaceutical Legislation and its likely impacts upon the EU biopharma ecosystem.

The opinions included in this work are those of Vital Transformation BVBA and are not necessarily those of the project's sponsors. The analysis was performed by Vital Transformation's Consulting Economist Dr Harry P. Bowen, Research Partner Gwen O'Loughlin, and CEO Duane Schulthess.

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The data used in this analysis can be accessed here.

Source of the data used in this research includes:

- OECD
- US Securities and Exchange Commission 10-K, 10-Q, 8-K, and 20-F Reports
- BioCentury
- Biomedtracker Citeline
- Pitchbook
- Eurostat
- IQVIA MIDAS: Country-level pricing data for France, Germany, Italy, Spain, Switzerland, and the United Kingdom.

VT Drug Test Cohort – SPC, RDP, and Orphan Status

Therapy	EU Approval Date	EU Patent Expiration	SPC IP Extension§	8 Year EU RDP Data Protection	2 Year RDP Market Protection	Orphan
ADEMPAS	3/27/2014	4/24/2023	4/24/2028	3/24/2022	3/24/2024	Yes
APTIOM	4/21/2009	6/28/2016	6/28/2021	4/21/2017	4/21/2019	
BLINCYTO	11/23/2015	11/23/2024	11/26/2029	11/23/2023	11/23/2025	
BRIDION	7/25/2008	11/22/2020	7/28/2023	7/25/2016	7/25/2018	
BRIVIACT	1/13/2016	2/20/2021	2/20/2026	1/13/2024	1/13/2026	
CALQUENCE	11/5/2020	7/11/2032	11/5/2035	11/5/2028	11/5/2030	
DARZALEX	5/20/2016	9/25/2027	3/22/2031	5/20/2024	5/20/2026	Yes
EDURANT	11/28/2011	8/8/2022	11/27/2026	11/28/2019	11/28/2021	
EPIDIOLEX	9/19/2019	8/13/2022	6/15/2025	9/19/2027	9/19/2029	Yes
EVENITY	12/9/2019	4/28/2026	4/27/2031	12/9/2027	12/9/2029	
JARDIANCE	5/22/2014	3/11/2025	5/26/2029	5/22/2022	5/22/2024	
KEYTRUDA	7/17/2015	6/13/2028	7/20/2030	7/17/2023	7/17/2025	
LUTATHERA	9/26/2017	5/20/2012		9/26/2025	9/26/2027	Yes
LYNPARZA	12/16/2014	3/12/2024	3/11/2029	12/16/2022	12/16/2024	
OFEV	1/14/2015	10/8/2020	10/8/2025	1/14/2023	1/14/2025	
OZEMPIC	2/8/2018	3/20/2026	3/19/2031	2/8/2026	2/8/2028	
SKYRIZI	4/26/2019	11/2/2031	4/25/2034	4/26/2027	4/26/2029	
TRADJENTA	8/23/2011	8/17/2023	8/29/2026	8/30/2019	8/30/2021	
TRESIBA	1/20/2013	7/22/2024	7/22/2028	1/20/2021	1/20/2023	
VIIBRYD	Not approved in EU					
XARELTO	9/30/2008	12/10/2020	4/1/2024	9/30/2016	9/30/2018	
XOFIGO	11/13/2013	12/16/2019	12/16/2024	11/13/2021	11/13/2023	
ZEJULA	11/16/2017	1/8/2028	11/19/2032	11/20/2025	11/20/2027	Yes
RELVAR ELLIPTA	11/13/2013	7/2/2022	11/13/2027	11/13/2021	11/13/2023	
BRILIQUE	12/3/2010	12/2/2019	12/1/2024	12/3/2018	12/3/2020	

§ As an SPC is generally required to be filed within 6 months of marketing authorization within the EU, SPC dates have been identified from the UK Intellectual Property Office (www.ipo.gov.uk), and the Intellectual Property Office of Ireland (eregister.ipoi.gov.ie).

EU company founding regression output

Fit

N	13
Mean of Y	3.555638020
Equation	Ln Founded = 4.606 + 1.206 Ln Beta EUR YR
R^2	0.683
R^2 adjusted	0.655
RMSE	0.391991030

Parameter	Estimate	95% CI		SE	t	p-value
Constant	4.606	4.074	to 5.137	0.24136	19.08	<0.0001
Ln Beta EUR YR	1.206	0.6615	to 1.751	0.24759	4.87	0.0005

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.

Effect of Model

Source	SS	DF	MS	F	p-value
Difference	3.648182107	1	3.648182107	23.74	0.0005
Error	1.690226648	11	0.153656968		
Null model	5.338408755	12	0.444867396		

EU Investment regression output

Fit

N	9
Mean of Y	9.996451128
Equation	Total Deals Lagged = 1.464e+04 * 2.456 Beta
R^2	0.700
R^2 adjusted	0.657
RMSE	0.127047782

Parameter	Estimate	95% CI		SE	t	p-value
Constant	9.591	9.334	to 9.849	0.10890	88.07	<0.0001
Beta	0.8985	0.3723	to 1.425	0.22253	4.04	0.0049

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.

Effect of Model

Source	SS	DF	MS	F	p-value
Difference	0.263133357	1	0.263133357	16.30	0.0049
Error	0.112987972	7	0.016141139		
Null model	0.376121328	8	0.047015166		

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