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The EU General Pharmaceutical Legislation:
calculated impacts – by design and unintended.

April 18, 2024

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Executive Summary

- The European Commission's 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. Under some scenarios, innovators may have the ability to extend regulatory data protections to 12 years.
- The challenge for investors and drug developers is that there is never a 100% certainty that patent protection alone will satisfy the length of time to develop a drug.
- Shortening regulatory data protections 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've undertaken an investment which, at minimum, will take 10 years on average before the EMA grants a new drug's approval.

Key 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 financial impact of -€1.22 billion Euros (-$1.3 billion USD).
- The European Commission has estimated that over 30% of all current EMA approved therapies will see revenues impacted by reducing RDP by 2 years; we find a 15% drop (-$64 billion) in total EU revenue in our 24-drug cohort, 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

- If 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 of over -$400 million USD.
- If every company in our cohort were 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 in part by US Corporate tax changes. Adding market uncertainty with changes to RDP will further negatively impact the EU biopharmaceutical ecosystem.
- The proposed amendments to the GPL projects a decrease in EU biotechnology startup firms from 19 in 2024 to 4 in 2030.
- 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.
- The incentives 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.

Background

- The European Commission has proposed a significant revision of the General Pharmaceutical Legislation (GPL), which aims to achieve the following main objectives:
    - Ensure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines.
    - Guarente security of supply and ensure medicines are available to patients in all 27 EU member states.
    - Offer an 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.
- To achieve these objectives, the EU commission has proposed various 'incentives' to innovative companies and investors.
- Vital Transformation (VT) has been asked by a multi stakeholder consortium to analyze the European Commission's GPL proposal, including its incentives, to determine the regulation's likely outcomes and consequences, both by design and unintended.
- Previous VT research has shown measurable declines in the EU biopharma ecosystem relative to the United States, as government price controls on medicines have expanded in Europe – this study places these trends into the context of the EU's revised GPL.

Scope

The Economic team of Vital Transformation VT will:

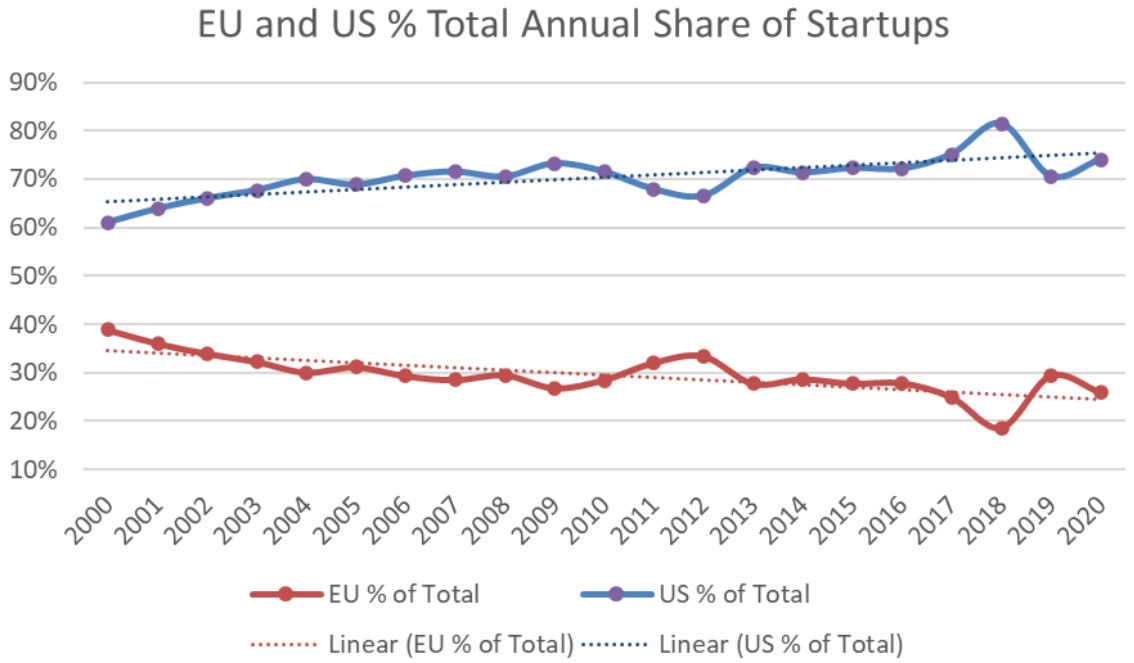
1. Develop a baseline assessment of the current comparative EU and U.S. biopharma ecosystems in 2023.
2. Determine the future competitiveness of the EU biotech ecosystem in the context of a two-year reduction in regulatory data protection (RDP) as proposed in the GPL, paying specific attention to its:
    a) Predated impacts on future EU investments
    b) Likelihood of a company bringing a drug to market in Europe
3. Quantify the combined impacts of the proposed GPL with currently evolving EU member state policies regarding price controls and financial 'clawback' mechanisms, and how these will impact the EU's biopharma ecosystem.
4. Estimate the value of proposed incentives included in the GPL, including extra market exclusivity periods and AMR certificates, and assess likelihood of their utilization and determine their value.

Methodology

1. VT selected a drug 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.
2. VT has obtained sales data in France, Germany, Italy, Spain, Switzerland, and the United Kingdom the cohort.
3. Using this sales data, VT modeled the economic impacts of clawbacks both alone and in combination with provisions of the GPL regarding changes to RDP, on the willingness of a company to bring a drug to market and the likely impact of these policies.
4. VT also modeled the economic and financial impacts of the various proposed incentives included in the GPL, and estimated their likely impacts upon EU metrics including:
    - Biopharmaceutical company formation
    - IP creation
    - VC/Industry investments
5. The raw data used behind this analysis is available for viewing here.

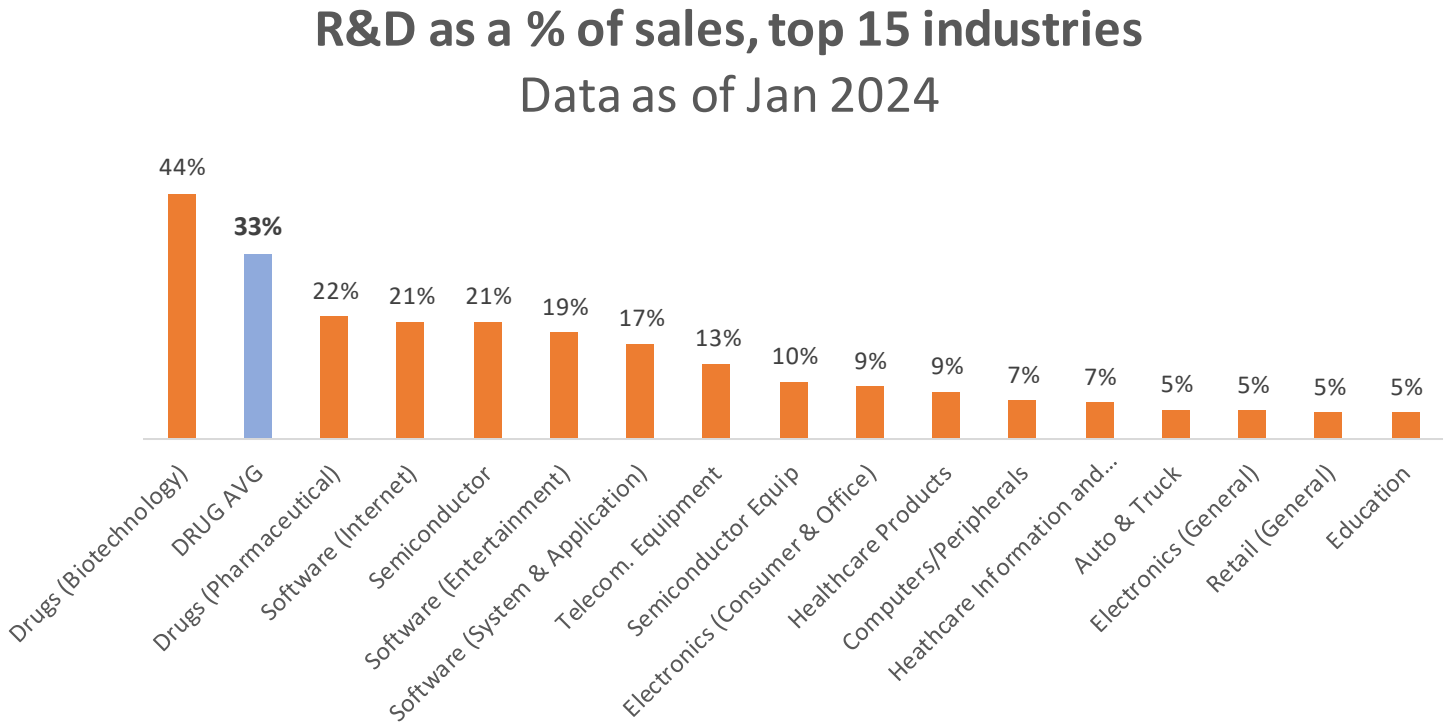
*One of the drugs in our cohort, although one of the top selling drugs globally, was not available in any of our 5 countries for which we had EU country specific sales data, thus, our cohort is limited to 24 therapies.

EU and US biopharma startups are diverging



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% ($p < 0.01$)

Industry in 2023 spent 33% of its sales revenues on R&D



Source - NYC Stern School of Business

Revenues determine where and how much R&D occurs

For every 10% reduction in EU sales, we see substantial losses in EU competitiveness as measured via KPIs.
All results are statistically significant

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%	06.11% - 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%

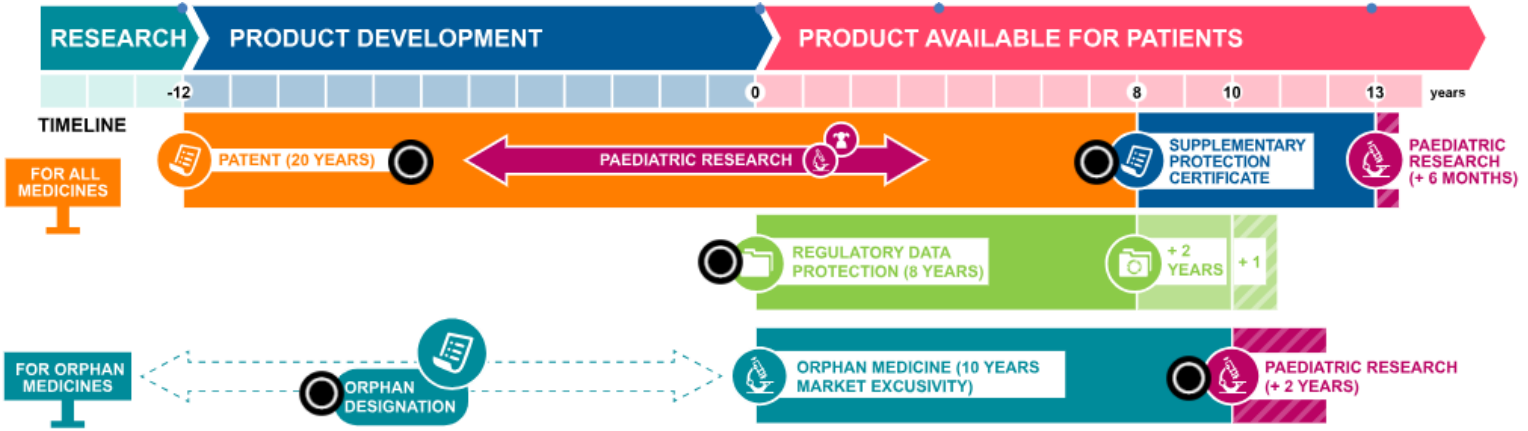
N = 66; *** p<.001

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.

Measuring the impact of proposed changes to regulatory data protection

The role of patents, SPCs, regulatory data protection, and market exclusivity in developing new medicines



- A new drug is protected by overlapping regulatory pathways which create certainty for investors and developers.
- As product development is often 6 – 10 years, a system of supplementary protection certificates (SPCs) was implemented whereby companies can apply to restore patent time lost to up to 15 years from the date of marketing approval.
- 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.
- During the 8-year period, a generic or biosimilar producer is not allowed to rely on the data of the innovator to support a follow-on marketing application.

Source: https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/

Proposed Changes to Regulatory Data Protection

- The European Commission has proposed in their revised general pharmaceutical legislation that it will replace the current 10 years 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 market authorization under terms defined as Bolar Exemptions, where they have access to an innovator company's RDP.
- According to a European Commission assessment, roughly 30% of all EMA approved medicines will see reduced revenues with a 2-year reduction in RDP.
- The EU Commission has proposed 'incentives' that will allow up to 12 years of data protection, assuming the innovator company meets several guidelines and criteria.
- In this research, we estimate the impact of a two-year loss of RDP, and the practicality of exercising these various incentives at the firm level to 'gain back' those lost 2 years or more of RDP.

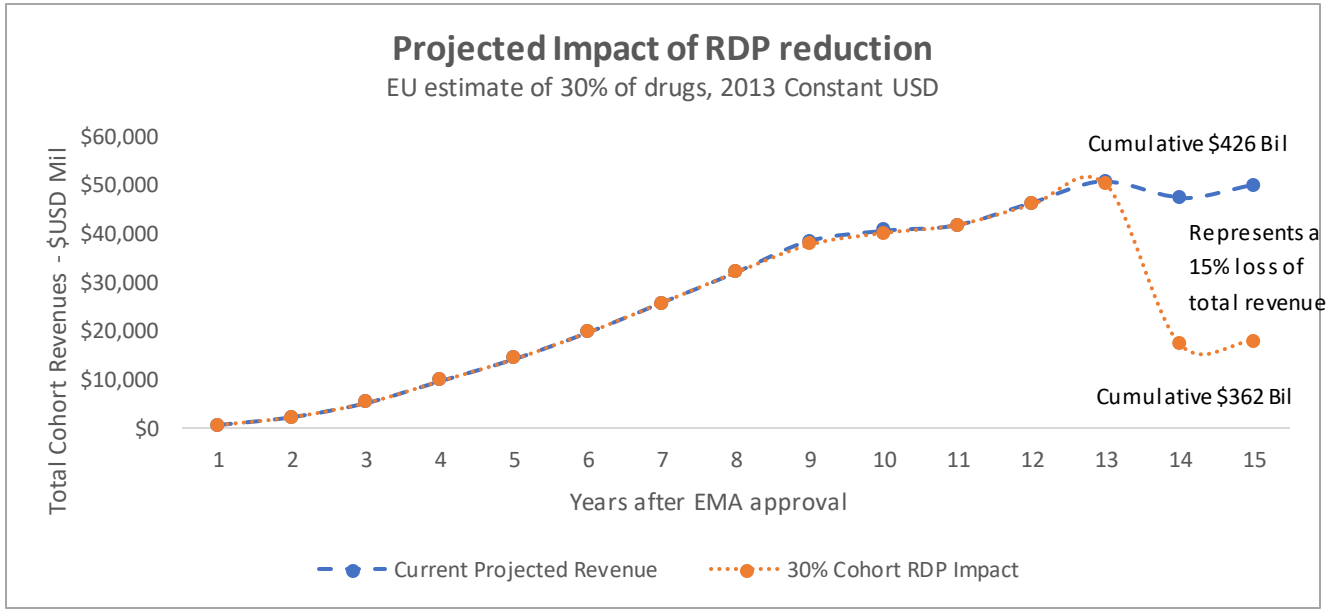
*The +1 year of additional market protection may be available in a case of a new therapeutic indication which brings significant clinical benefit in comparison with existing therapies, this extra year is awarded on a case-by-case basis and is not guaranteed during a drug's development.

Direct Impact of proposed EU RDP changes

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%

- Two therapies in our 24-drug cohort are directly impacted by a two-year loss of lost RDP.
- Lost RDP creates losses of €1.2 Bil EUR in direct revenues.
- What is not calculated are the long-term unintended consequences due to increased risks and market uncertainty created by attacks on RDP.

Companies lose 15% of total EU revenues due to 2 years of RDP loses



- While only 8.3% of our test cohort is directly impacted by a 2-year loss of RDP, the European Commission has estimated that over 30% of therapies will see revenues impacted by a 2-year loss of RDP.

- If we apply this 30% of therapies impacted to our cohort, we see a 15% drop in total EU revenue (measured in constant 2013 USD), from a total of $426 bil to $362 bil - $64 billion in total.

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

Clawbacks Overview

- According to a 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."

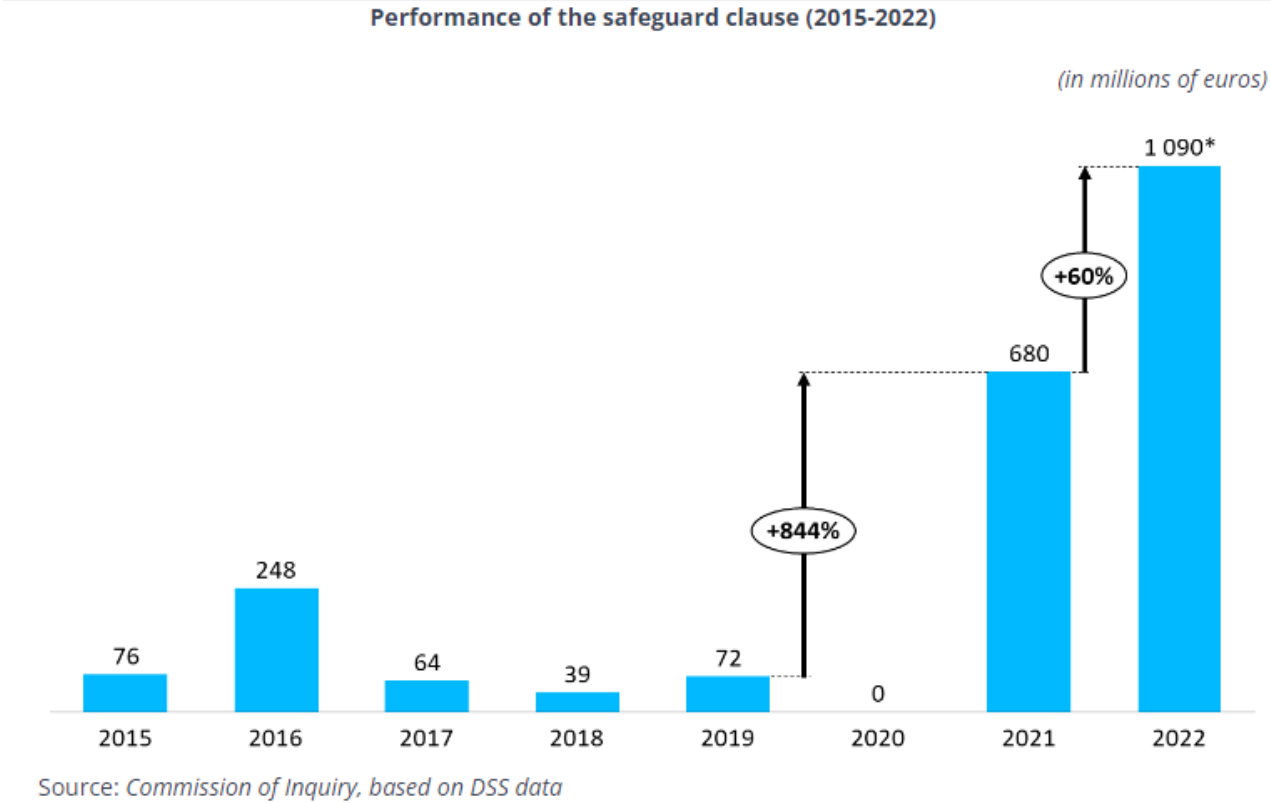
- Increasingly, many EU governments have put restrictions on the annual budgets of pharmaceutical products, limiting increases in spending to the rate of inflation.

- These policies ignore radical demographic changes in the EU which are driving up the rate of utilization and spending apart from inflation; in Germany in 2012 there were already only two workers per pensioner.

- According to VT's calculations, the annualized growth in EU clawback provisions in our 24-drug cohort exceeds the growth in annual drug sales by 20%

- What does this imply for the impact of these price controls on the EU market for pharmaceuticals?

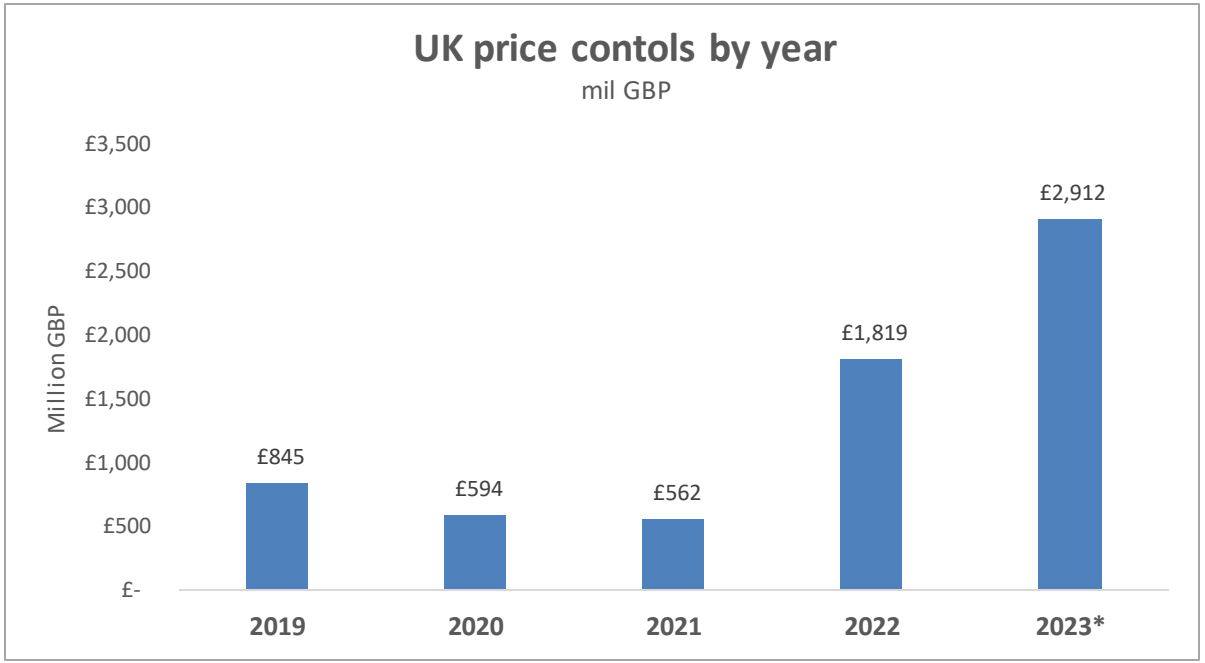
The growth in French clawbacks exceeds 900% since 2015



Source: French Senate Commission of Inquiry on the increase of clawbacks, July 2023, Mil EUR Senat.fr

Price Controls – increasing clawbacks in the UK

UK clawbacks in 2023 were nearly 30% of sales



Source: gov.uk

* 2023 impact has been projected upon three quarters of data

In February of 2023, the UK pharmaceutical industry requested that, "the government to scrap plans to raise the statutory revenue clawback rate from 24.4% to a record 27.5%"

In November of 2023, Britain's pharmaceutical industry and the UK government agreed to new clawback terms under the voluntary scheme for branded medicines pricing, access and growth ("VPAG"), which assumes a growth rate of 4%.

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 at both maintaining a fair price control whilst not impairing innovative capital..

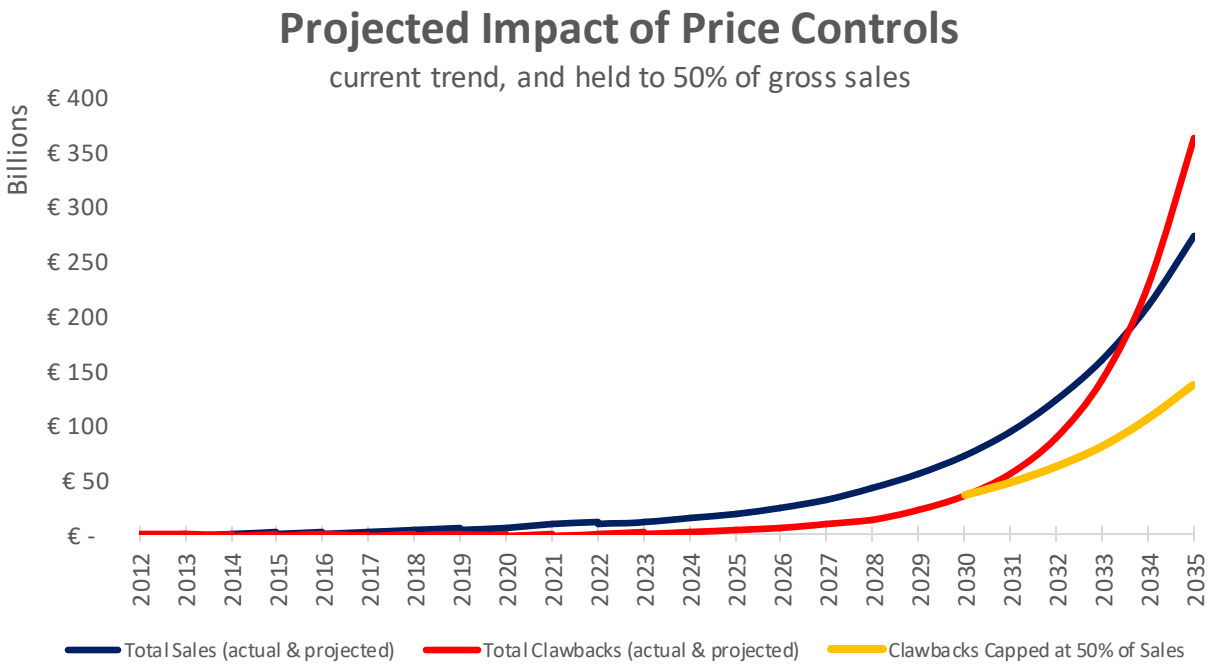
24 drug cohort – impact of price controls by market

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

- While variable by market, clawbacks are increasing in general, taking up a larger percentage of EU net revenue.
- The challenge for an innovator company is that these clawbacks are demanded by EU member states often a year or more AFTER those revenues have been booked by the companies.
- As of July of 2023, the French clawbacks based upon 2022 sales had not been confirmed – this radically increases the market uncertainties for investors and innovators.
- 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.

Price controls will exceed 100% of sales by 2033

Assumes revenue growth and clawback policies are held constant



- The growth rate in clawbacks currently exceeds the increases in sales by roughly 20% per year in our 24-drug cohort.
- 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.

Estimates based on data for 5 countries (France, Germany, Italy, Spain, Switzerland and United Kingdom) over 11 years (2012-2022). Values in constant 2015 EUR. Projected values starting in 2024 use median annual growth rates: Sales = 27% per year; Clawbacks = 47% per year

Measuring the impact of RDP incentives

The EU has proposed a series of incentives to 'gain back' RDP

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.

- +2 years for medicinal products supplied in all EU 27 Member States within a 36-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
  - there is no medicinal product authorized in the EU for such disease with a high morbidity or mortality;
  - 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.

As many of these 'incentives' incur large upfront investments by a company, with no guarantee of success, VT has calculated the potential ROI and likelihood of the companies in our cohort exercising these RDP extensions.

The EU has proposed a series of incentives to 'gain back' RDP

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VT computed the cost of entering the "average" EU country based on data (shown) for 20 EU countries. Using the data shown, the average NPV of entry costs was calculated as the cost to meet the RDP incentive criteria.

Country	1 lawyer	1 lobbyist	2 Office Assitants	Rental Cost per sq meter*	Up-fit Cost per Sq Meter*	Variable Cost (2013 USD)	Fixed Cost (2013 USD)
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
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

* assumes 150 sq meter office

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)**

- Our 24-drug cohort has 13 firms that would need to make large scale country investments for access.
- We calculate the impact across the entire cohort.
- The total loss for our cohort is roughly $400 million euros, $31 million per frim.

Result 2: NPV for our 24 drug cohort of gaining 4 years of RDP, 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)**

- We've assumed a total of 12 years of RDP requires no further investments beyond what's already been spent to access all 27 member states – this is highly optimistic.
- We calculate the impact loss across the entire cohort for all 13 companies increases to $ -1.2 billion.
- The challenge from a strategic standpoint is the infrastructure to support these incentives needs to be in place before a drug is approved – this will be seen as an added cost to the investment, with an uncertain ROI which occurs at the END of the payback period, when the revenues are the most discounted.

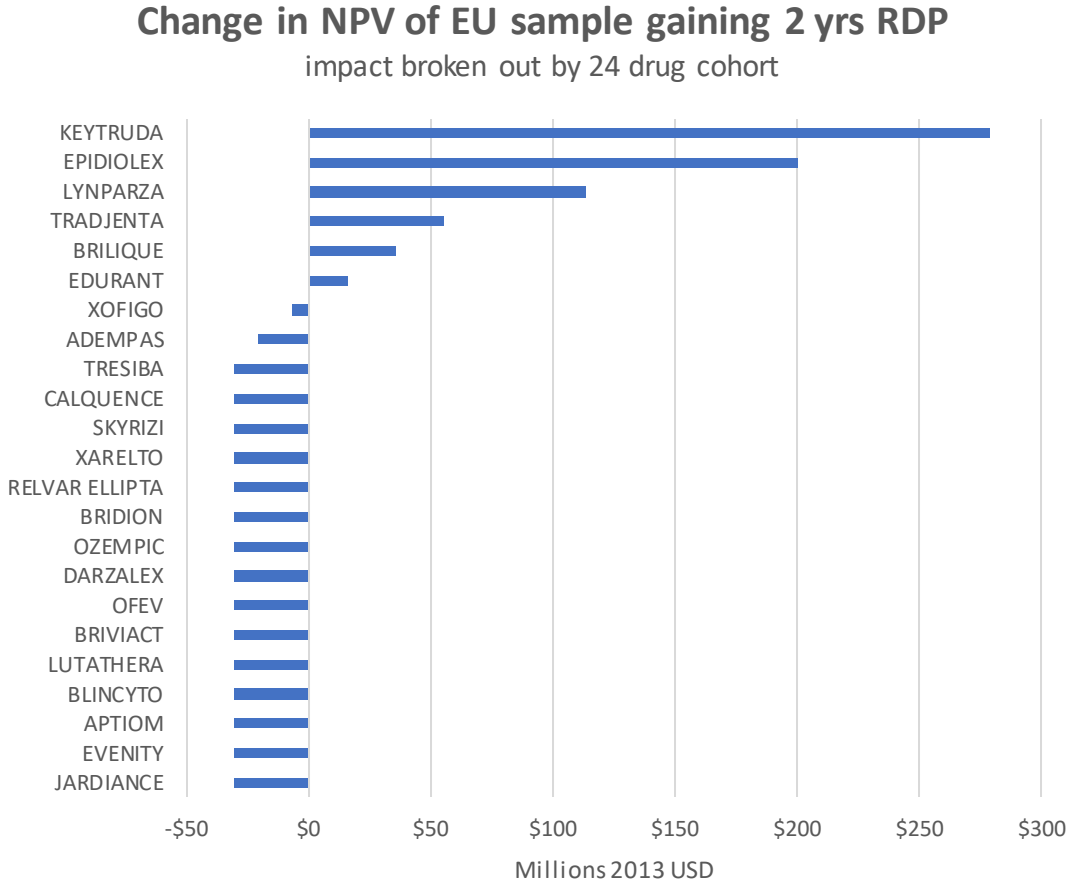
Result 3: NPV of 24 drug cohort, RDP impacting 8 drug EU random sample

- The EU has stated 30% of all approved patented therapies will be impacted by RDP reductions under the GPL
- Using our previous random sample of 8 drugs we can model a theoretical NPV of investing in market access in all 27 member states to increase their RDP from 8 to 10 years.
- We assume an 11% cost of capital.

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**

- The NPV is modestly positive
- This result shows an average impact across all 24 drugs in our cohort, what is the impact of this NPV model on a drug-by-drug basis?

Result 3: NPV of 24 drug cohort, RDP impacting 8 drug EU random sample



- Keytruda and Tradjenta were included in our random sample of 8 drugs modeling EU's statement that 30% will be impacted by RDP reductions in the GPL.
- The aggregate sales for those drugs swamps any costs that are incurred by the rest of our cohort; those losses are 'hidden' when the cohort impacts are expressed as an average.
- Only 6 of our 24 therapies have a positive NPV when the impacts are calculated on the individual drug and firm level - the NPV is negative for most of our therapies.
- The investments to support these 'incentives' need to be in place before a drug is approved by the EMA - this will be an added cost increasing risks.

The impacts of the 2018 U.S. corporate tax legislation on EU biopharma

The EU has seen a significant drop in biopharma firm creation

large drop occurred in 2018

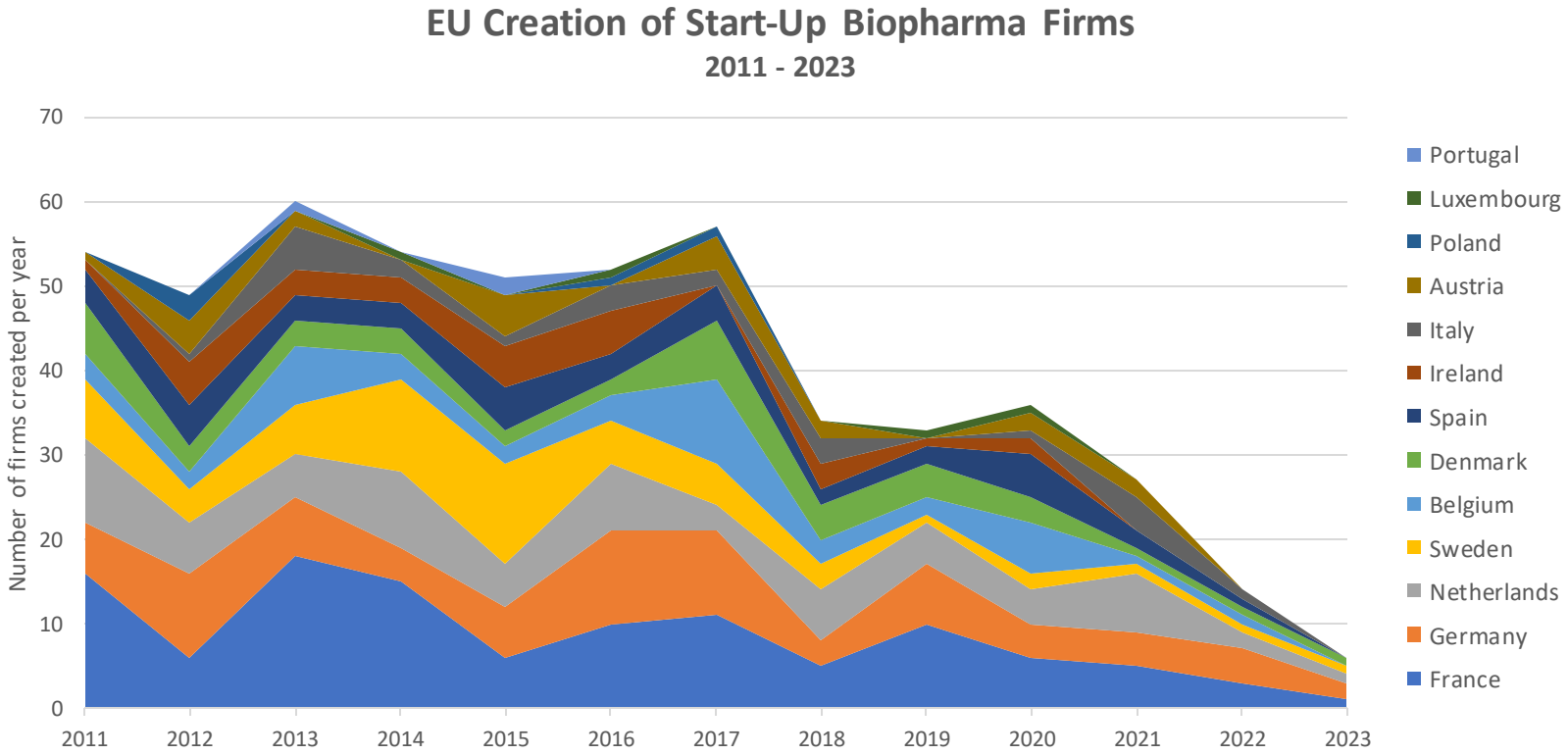
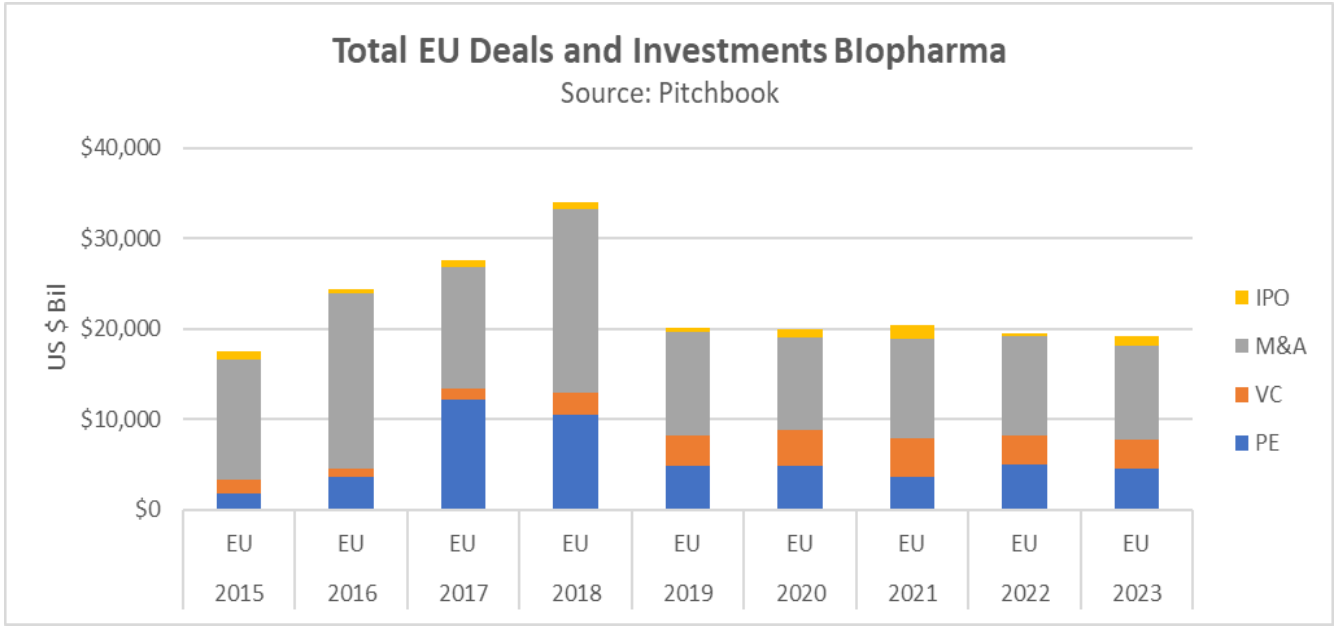


Figure 13 Source - Biomedtracker

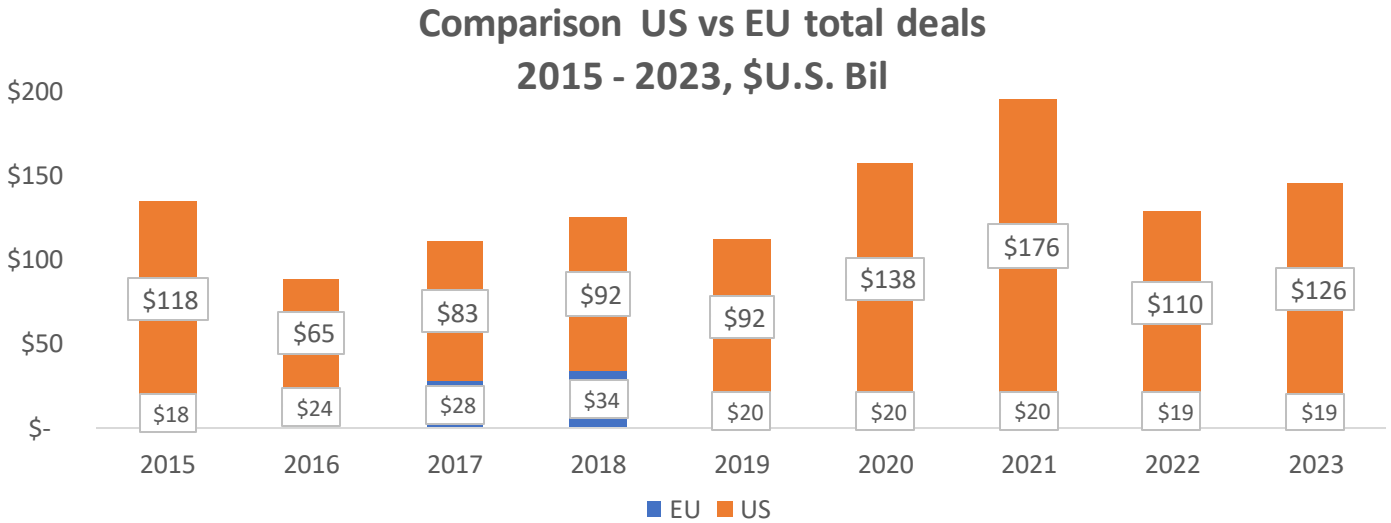
2018 US corporate tax changes negatively impacted EU investments



- We see a marked and substantial drop in EU biopharma investments in 2019 before the COVID-19 pandemic.
- Prior to the 2018 U.S. Tax and Jobs Act, U.. firms held $777 billion abroad, those funds were often used for strategic partnerships and acquisitions within the EU.
- In 2018, U.S. corporate taxes were equalized with EU levels.

Source –Pitchbook, total EU biopharma deals < $10 billion in size.

Current size and scope of the EU and U.S. biopharmaceutical markets



- U.S. dealmaking, nearly doubled through 2021; we attribute the drop in 2022 to the introduction of the Inflation Reduction Act (IRA) legislation in June of 2021.
- The EU sees a marked decline from 2018 – 2019, and a continuing decline since.
- Any policy prescriptions in the EU which harm its global competitiveness will only add to the disequilibrium that is currently observed.

Source –Pitchbook, total EU biopharma deals < $10 billion in size.

Estimating ecosystem uncertainties created by the GPL revision

Measuring increased risks/uncertainties in the EU

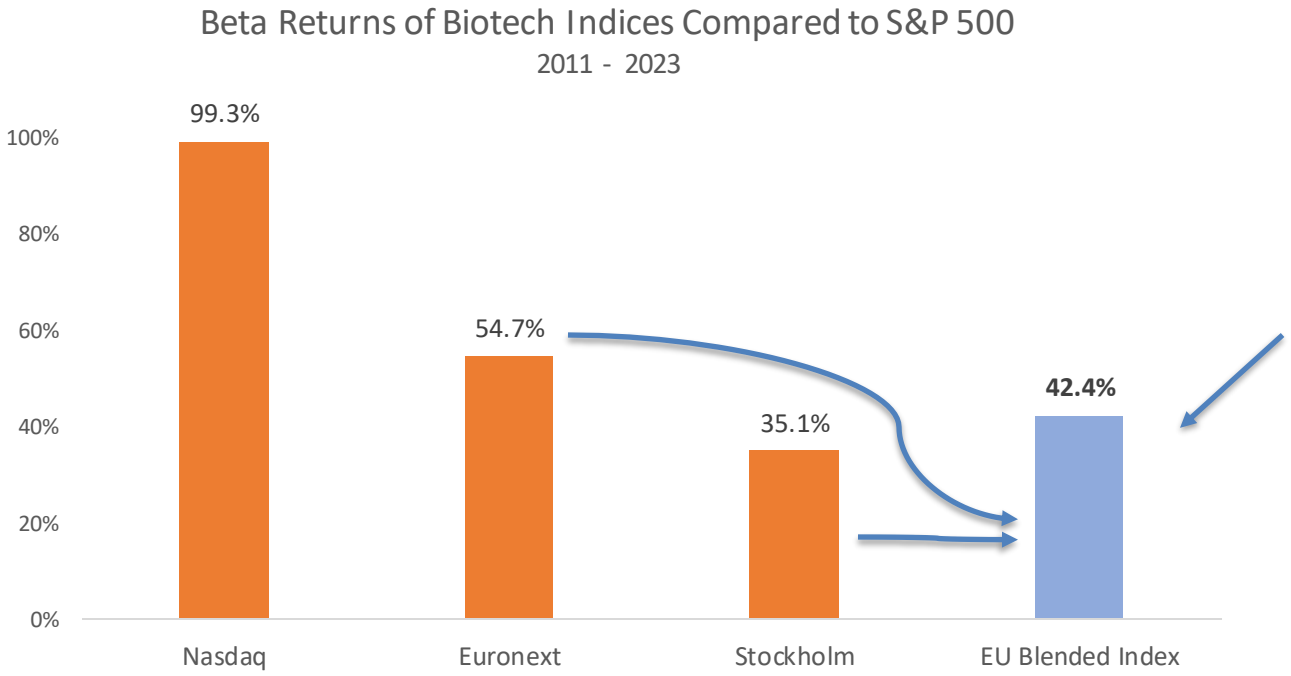
modeling investor behavior

- One of the challenges prognosticating future events is finding a quantifiable and measurable way to determine how people will react to an event which has not yet occurred.
- 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.

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

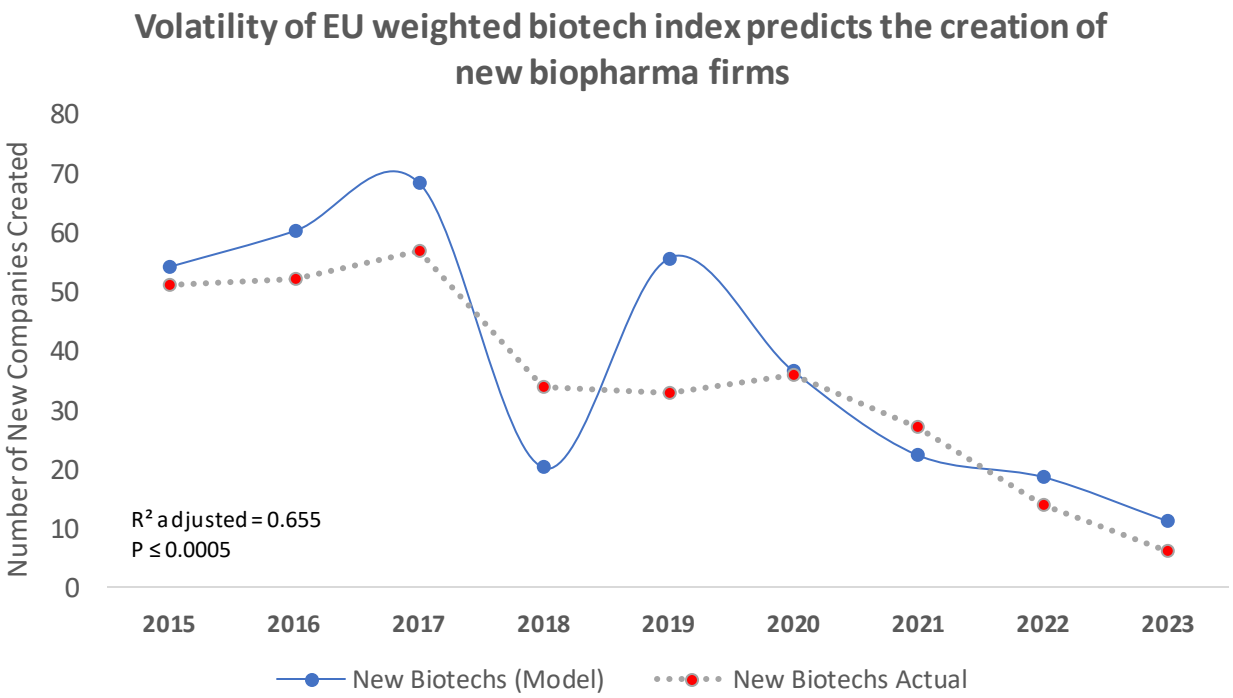
- A market β measures the volatility of the returns of an investment asset, or a portfolio of investment assets like an index fund, relative to a 'global' market benchmark such as the S&P.
- We find the beta 'β' by calculating the covariance between the return (r_a) of a stock or index and the return (r_b) of another stock or index divided by the variance of the other index over a period of several years.
- 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, providing insights as to how investors will respond.

Biotech market returns



- VT has created a 'blended' weighted β index tracker of the Scandinavian and Euronext biotech markets, which represents roughly 60% of all publicly traded EU-based biotech firms.
- This EU blended index has returned 42.4% of the S&P 500, while the Nasdaq biotech index has nearly equaled (99.3%) the returns of the S&P 500.

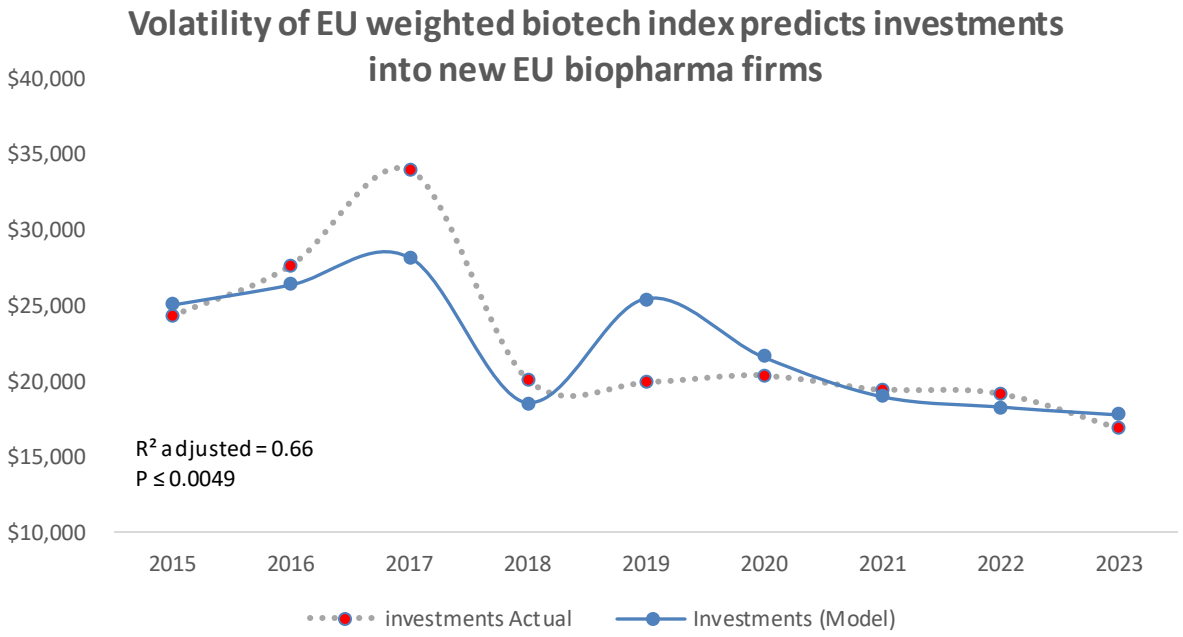
EU blended β accurately predicts EU biotech company creation



- Our EU index β measuring investor behavior predicts with good accuracy the correct number of companies that have been created in the EU.
- We can now use this model to anticipate investor risk appetite and measure its potential impact on future EU biotech company formation.
- It should be noted that we both predict and accurately measure a substantial reduction in EU company creation since 2017.
- Our countries in scope include France, Germany, Netherlands, Sweden, Belgium, Denmark, Spain, Ireland, Italy, Austria, Poland, Luxembourg, and Portugal

Source: Biomedtracker

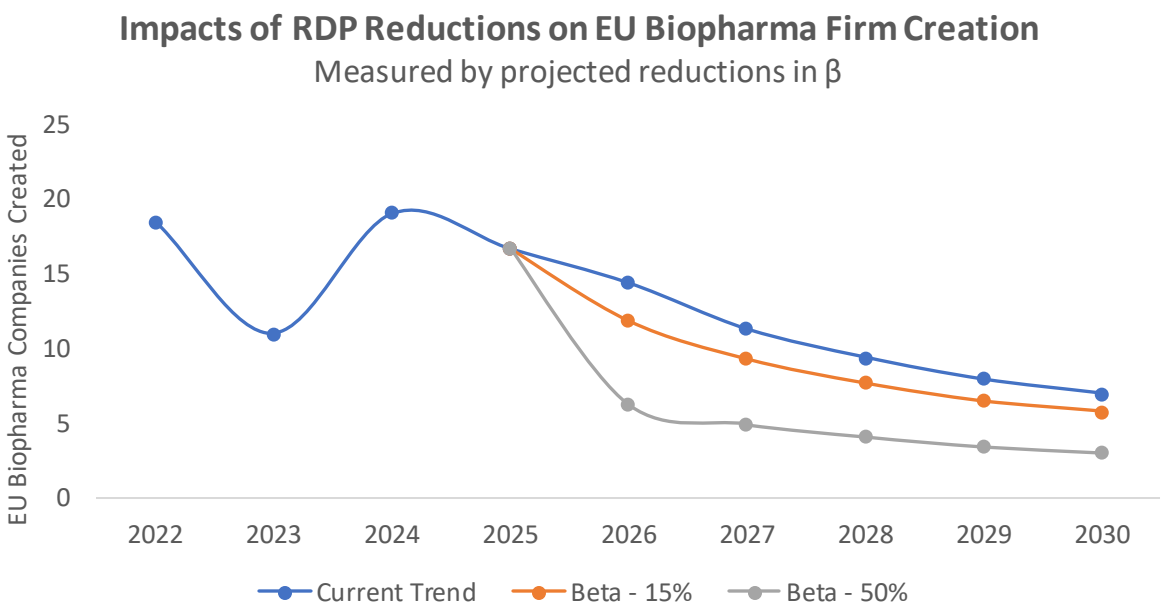
EU blended β accurately predicts biotech deals and investments



- Our EU index β measuring investor behavior predicts with good accuracy the total amount invested annually in biotech deals the EU.
- We can now use this model to anticipate investor risk appetite and measure its potential impact on future EU biotech investments.
- It should be noted that we both predict and accurately measure a substantial reduction in EU investments since 2017.
- Our deal search was restricted to the EU 27, and does not include Switzerland, Norway, or the UK.

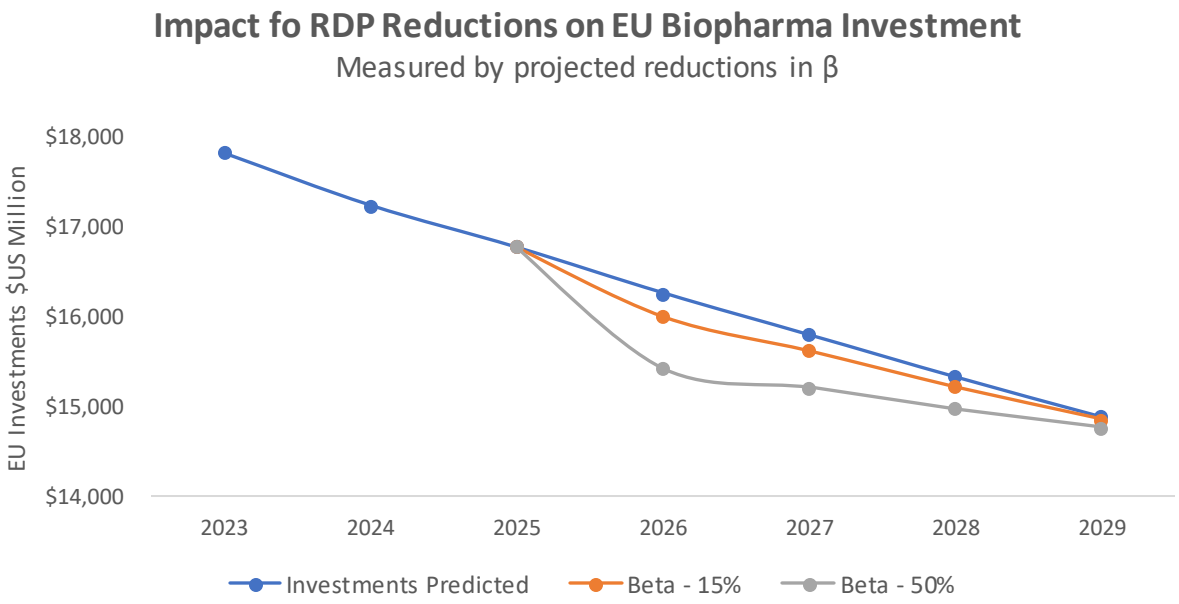
Source: Pitchbook, EU deals < $10 billion. For analysis, the impact of beta on investments is lagged by one year and accounted for in our regression model. This chart shows actual investments advanced by one year to visually indicate this timing of impacts.

Projected losses in EU company creation due to RDP changes



- Our model based upon Biomedtracker data only projected 11 EU biopharmaceutical startup firms in 2023.
- 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.
- The EU created 60 Biopharmaceutical startup firms as recently as 2017; 2023's total of only 13 companies founded represents a 78% decrease in EU startup firms over 6 years.
- If investors interpret the GPL to mean higher risk, our model predicts between 3 to 7 EU biopharmaceutical startup firms in 2030.

Projected losses of EU investments due to RDP changes



- Based upon the EU Commission's own assessment of >30% of companies impacted by reduced RDP, we can use our model to predict how investors will react.
- We use our previous calculations showing a real 15% revenue reduction across our cohort, and a marked increase of investor risk as seen in 2018 with changes to U.S. equating to roughly a 50% decrease in β.
- The challenge for regulators is that there is little scope for any increase in risk which lowers sector investments given current EU trends.
- The declines in the market projection 'catch up' to the modelled decline in β volatility as those declines are already acute.

Conclusions

- The is never 100% certainty that patent protection alone will satisfy the length of time to develop a drug; altering data protections will be a strong signal that investments bear higher risk due to future regulatory changes, and investors will alter their behaviour, including exiting the market.
- The downward trends in European life sciences indicators dating back to 2018 have had a demonstrably negative impact on EU biopharma competitiveness; increasing market uncertainty with changes to RDP will compound these problems.
- 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 -€1.22 billion Euros ($1.3 billion USD)
- 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 find that the current EU incentives to extend RDP after a reduction to 8 years (6+2) from 10 will have little positive impact; our NPV calculations are nearly universally negative and it is doubtful that any innovator, particularly a small biotechnology firm dedicating 44% of its cashflow to R&D, will exercise such an 'incentive'.
- The challenge for a drug developer is that these incentives need 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.
- 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, This is reflected in a precipitous drop in EU biopharmaceutical startup firms, which have virtually come to a standstill in the last 24 months.

Disclosure

- 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.
- This project was made possible with the financial support of the Biotechnology Innovation Organization (BIO), AbbVie, and Amgen.

Appendix

Data Sources Used

Datasets used in this research include:

- OECD
- US Securities and Exchange Commission 10-K, 10-Q, 8-K Reports
- BioCentury
- Biomedtracker Citeline
- Pitchbook
- Eurostat
- IQVIA MIDAS: EU 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

VitalTransformation

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: $\beta = 0$
The parameter is equal to 0.
H1: $\beta \neq 0$
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

VitalTransformation

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: $\beta = 0$

The parameter is equal to 0.

H1: $\beta \neq 0$

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		