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INVESTIGATION

From blockbuster to "nichebuster": how a flawed legislation helped create a new profit model for the drug industry

Twenty years ago, the EU passed a law to motivate the drug industry to develop medicines for rare diseases. But a system intended to help patients with neglected maladies primarily turned into a corporate cash machine. Daan Marselis and Lucien Hordijk report

Daan Marselis, Lucien Hordijk

After reaping 12 years of orphan exclusivity rewards in Europe, company executives at Celgene (now Bristol-Myers Squibb) were on the verge of celebrating yet another monopoly extension. If the European Medicines Agency (EMA) authorised Celgene's latest orphan application for lenalidomide (Revlimid), the company would obtain a fourth orphan designation for its crown jewel—prolonging "market exclusivity" of this famous oncology drug.

Lenalidomide is not a typical rare disease treatment. It is derived from thalidomide, the notorious molecule that was pulled from the European market in the 1960s for causing birth defects. After a few molecular tweaks lenalidomide was launched and became one of the most profitable orphan medicines ever marketed. Our data show that, up until 2019, lenalidomide made €55bn (£50bn; $64bn) in worldwide sales.

Why would the EMA consider rewarding this already very lucrative product with yet another 10 years of market exclusivity—an incentive package meant only for drugs that would otherwise not be profitable?

We have analysed two decades of sales data and found that companies have reaped billions of profit off the back of orphan drug designations (box 1). The European Commission is set to publish a review that suggests most of these drugs would have been launched anyway without favourable monopoly rights. The findings could lead to reform in Europe.

Box 1: How the Investigative Desk conducted its investigation

Our list of orphan products is based on the datasets published by the EMA and FDA. We limited the scope to the 2000-19 period. We included all medicines that were given orphan status by the EMA. If the orphan status expired (or was withdrawn) by the manufacturer, we still considered the product to be an orphan medicine.

Revenue and sales data were derived from annual reports and fourth quarter and full year's earnings releases provided online by public companies. Revenue and sales for the year 2019 came from the annual reports, unless specified otherwise. We could not find sales data for products marketed by private (not publicly listed) companies.

Companies can report sales, net sales, revenue, and net revenue. Sales (and revenue) are gross sales. Net sales (and net revenue) are total revenue less the cost of sales returns, allowances, and discounts. We made a note of this in our database, but otherwise chose to ignore, as companies typically don't report the value of sales returns, allowances, and discounts. Drug companies typically only disclose sales data for products that are considered "financially material" or that are key drivers of their business and strategy. They do so to inform and attract investors. It was not possible to estimate profitability, as companies do not specifically disclose investments in developing an orphan medicine.

For the "first to market" date, we used the date of the first market authorisation either in the EU (EMA) or the US (FDA). For this information we used datasets provided by the EMA and FDA.

We accumulated product sales on the level of the brand name of the product (eg, Imbruvica). This is important with respect to products that are marketed by multiple companies or have changed ownership over time. When we calculated the total sales of a product that is marketed by multiple companies, we did not correct for sales/net sales differences. Some companies report fiscal years not ending on 31 December but at the end of March, June, or September. We did not correct for this.

In the database, we use the currency that is used by the companies. We calculated the value in euros using historical exchange rates provided by the European Central Bank. We used the exchange rate of the exact date the fiscal year ended (be it at the end of December, March, June, or September). In cases where the fiscal year ended during the weekend or on a bank holiday, the European Central Bank's dataset would not provide a historical rate. We chose to use the exchange rate of the first business day before the official end date of the fiscal year.

Lucrative legislation

In the event, the EMA decided against the new orphan application for lenalidomide in December 2019. But its decision did not hinge on the fact that the product had already earned Celgene huge profits but because of inaccuracies in Celgene's assessment of the prevalence of the disease it was applying for. Economic considerations have never been a criterion in the EMA's assignments of orphan rewards to the industry, our investigation found, despite the fact that the presumed lack of profitability of medicines for rare diseases was the main reason to pass the orphan law 20 years ago.

This would explain why the European Union's orphan legislation seems surprisingly wasteful. An official, as yet unpublished evaluation of the policy ordered by the European Commission looked at the 146 orphan medicines introduced between 2001 and 2016.[1] It estimates that only 18-24 (12-16%) of them

are attributable to the policy. The majority would have probably reached the market anyway, which implies that more than 120 orphan medicines have been given superfluous monopoly rights. Moreover, the European review found that only 28% of the registered orphan medicines treat diseases for which there were no alternative treatment options. Meanwhile, 95% of rare diseases remain without treatment.

The European Commission does not want to comment on these findings until publication, though they were shared with the Pharmaceutical Committee, an expert group of EU advisers, at its meeting on 12 March.[1] The experts at this meeting were warned that the legislation risks "overcompensation," in particular of orphan medicines with multiple indications and old or known active substances, "where the investment was little in relation to the revenues obtained."

The EU orphan legislation has yielded lucrative results for the drug industry, helping companies transform the traditional blockbuster model into a "nichebuster" model, in which products treating diseases that affect only small patient groups still manage to generate more than a billion euros annually. The Investigative Desk (a non-profit organisation for investigative journalism) analysed global sales data of 120 (of 174) orphan medicines registered in the EU in the past 20 years. In 2019 alone, there were 20 such nichebusters with an orphan designation in the EU—up from three in 2009 (tables 1 and 2).

Table 1 | Number of nichebuster orphan drugs earning more than €1bn annually.

Financial year	Number of drugs
2009	3
2010	3
2011	3
2012	3
2013	4
2014	7
2015	8
2016	11
2017	11
2018	17
2019	20

Table 2 | Nichebuster orphan medicines with a revenue higher than €1bn in 2019.

Product	Revenue 2019 (€)
Revlimid	10 790 457 540
Imbruvica*	7 196 902 261
Soliris	3 512 907 246
Darzalex	2 668 684 351
Pomalyst/Imnovid	2 534 270 963
Jakavi/Jakafi†	2 491 426 781
Sprycel	1 878 226 811
Spinraza	1 866 654 798
Tasigna	1 673 342 234
Ofev	1 491 000 000
Xyrem	1 462 101 656
Afinitor/Votubia	1 366 266 133
Symkevi/Symdeko	1 261 944 098
Revolade/Promacta	1 260 347 130
Orkambi	1 185 589 283
Opsumit	1 181 235 535
Glivec	1 124 165 554
Eloctate	1 115 519 700
Lynparza	1 066 405 555
Esbriet	1 013 451 262

* Imbruvica is sold by Johnson & Johnson and AbbVie. †Jakavi/Jakafi is sold by Novartis and Incyte.

Since 2001, average annual sales of all orphans has multiplied by five, from €133m to €723m in 2019. Medicines treating rare cancers, like Revlimid, are particularly rewarding. Last year, revenues for oncology orphans averaged €1.1bn (with a median revenue of €539m), more than double the amount for non-oncology orphans that same year (tables 3 and 4). Celgene declined to comment on our findings.

Table 3 | Average revenue by year

Financial year	Average revenue (€)
2001	133 176 712
2002	256 602 377
2003	315 760 550
2004	266 355 949
2005	250 175 147
2006	238 905 293
2007	273 337 218
2008	309 618 882
2009	324 347 626
2010	349 282 584
2011	413 102 427
2012	426 607 555
2013	432 473 944
2014	469 396 314
2015	482 675 758
2016	529 595 493
2017	508 494 008
2018	538 026 201
2019	723 665 379

Table 4 | Top 10 products based on total revenue—of all time and since 2015

All time				Introduced since 2015		
Product	Category	Grant total		Product	Category	Grant total
Revlimid	oncology	55 315 168 034	1	Darzalex	oncology	6 033 860 952
Glivec	oncology	43 334 046 427	2	Orkambi	other	4 640 675 884
Imbruvica	oncology	21 005 583 753	3	Spinraza	other	4 152 991 943
Soliris	other	19 656 291 067	4	Jinarc/Samsca	other	2 544 798 152
Tracleer	other	13 503 397 816	5	Lenvima	oncology	1 962 517 695
Sprycel	oncology	13 138 317 644	6	Symkevi/Symdeko	other	1 933 260 255
Tasigna	oncology	11 990 718 479	7	Uptravi	other	1 527 370 742
Sutent	oncology	11 048 947 486	8	Strensiq	other	1 435 927 618
Afinitor/ Votubia	oncology	10 334 374 343	9	Ninlaro	oncology	1 130 789 123
Jakavi/Jakafi	oncology	9 348 984 606	10	Venclyxto	oncology	1 005 439 351

Origins of the orphan drug rule

So what's the origin of this generous legislation? In the late 1990s, European law makers feared that they were missing out on investment opportunities for the drug industry. The US and Japan had specific policies in place to motivate drug companies to develop treatments for "unmet needs," but the EU lacked a comparable incentive scheme.[2]

The European Commission followed through with its own orphan legislation in 1999. Heavily influenced by the US, Europe chose to reward companies that would bring rare disease treatments to the market with market exclusivity: a new reward for innovation. It guarantees that other product applications for the same therapeutic indication would be blocked.

Being at its core an industrial policy, the incentives had to be competitive with those of the US Food and Drug Administration (FDA). "In the United States, market exclusivity is currently seven years, so let's do better," said one of the highest ranking EU officials on pharmaceuticals at a workshop in 1998, "15 years would be better than 10 . . . and 20 would be better than 15."[3] When voted through parliament, the term was established at 10 years—though 14 medicines managed to extend their monopolies to over 15 or 20 years by combining multiple market exclusivities for different indications (table 5).

Table 5 | 14 orphan medicines have (had) market exclusivity surpassing 10 years (not counting possible extensions after filing a paediatric investigation plan)

Tradename	First authorisation in the EU	Last authorisation in the EU	Total duration of market exclusivity (years)	Annual revenue at time of latest authorisation (million euros)
Soliris	22 Jun 2007	28 Aug 2019	22.18	3.500
Revlimid	19 Jun 2007	12 Jul 2016	19.06	6.210
Carbaglu	28 Jan 2003	1 Jun 2011	18.34	7
Vyndaqel	18 Nov 2011	19 Feb 2020	18.25	421
Nexavar	21 Jul 2006	27 May 2014	17.85	736
Zavesca	21 Nov 2002	28 Jan 2009	16.19	35
Ofev	19 Jan 2015	20 Apr 2020	15.25	1.500
Adcetris	30 Oct 2012	19 Dec 2017	15.14	289
Tracleer	17 May 2002	11 Jun 2007	15.07	697
Glivec	12 Nov 2001	1 Dec 2006	15.05	1.500
Signifor	27 Apr 2012	21 Nov 2014	12.57	-
Yondelis	20 Sep 2007	30 Oct 2009	12.11	-
Gazyvaro	24 Jul 2014	15 Jun 2016	11.89	179
Torisel	21 Nov 2007	25 Aug 2009	11.76	-
Imbruvica	23 Oct 2014	7 Jul 2015	10.71	1.200

To obtain market exclusivity, companies have to prove that there is "no satisfactory" treatment for the indication that they are applying for, or, if such treatment does exist, that the new product offers a substantial benefit. The company also has to choose one of two routes. Either it proves that the product is intended to treat "a life threatening or chronically debilitating condition affecting not more than 5 in 10 000 persons" in the EU (the prevalence route), or it proves that without incentives, the medicine would probably not generate sufficient revenues "to justify the necessary investments" (the return on investment route).

According to Ellen 't Hoen, director of the non-governmental organisation Medicines Law and Policy, this distinction stemmed from early difficulties with the US Orphan Drug Act (1983). "Since there are no requirements for companies to provide data on development costs, the FDA found it very difficult to assess when a product would be profitable," she says. European law makers concluded that it would be easier to introduce a surrogate criterion of profitability. "They simply assumed that developing medicines for patient populations below 5 in 10 000 is not commercially viable," said 't Hoen.

Now, 20 years later, only one medicine has ever been designated an orphan medicine in the EU via the "return on investment route," though the company never commercialised the product. All orphan medicines that received market authorisation in the EU obtained their status via the prevalence route.

Safety catch disabled

Meanwhile, high prices of orphan medicines have caused increasing controversy in even the most prosperous EU member states. In 2016, the European Council observed that there were multiple examples of market failure "where patient access to effective and affordable essential medicines is endangered by very high and unsustainable price levels."

Studies have shown that access to orphan medicines in the EU is unequal. In rich countries like France and Germany patients have access to 63-90% of authorised orphan medicines, but in poorer countries where per patient expenditure on orphan medicines is much lower, like Greece, Bulgaria, Romania, and Croatia, access is only 27-38%.[4] The European Council recommended that the European Commission "consider revision of the regulatory framework on orphan medicinal products."[5]

One problem is that the European Commission doesn't have a corrective mechanism for misbehaviour, said 't Hoen. Theoretically, the EU can withdraw market exclusivity after five years. In the first drafts of the orphan legislation, this measure could be invoked by a member state in case the prevalence criterion was no longer met or if the company "demands a price for the product which cannot be justified."[6] But in the final version, market exclusivity can only be withdrawn if the criterion that was used for acquiring the orphan designation is no longer met.[7 8] Since companies only use the prevalence route in their applications, an "emergency break to counter overpricing has effectively been disabled," says 't Hoen.

Untouchable

The rewards of orphan drug status seem to last much longer than the official 10 years. A spokesperson for the European Commission told us that, of the 70 medicines with expired orphan status, less than 20% have since faced generic or biosimilar competition.

"Market exclusivity is basically untouchable," said Sven Bostyn, associate professor of biomedical innovation law at the University of Copenhagen in a telephone interview. Although patents, especially secondary use patents, are regularly annulled in courts, market exclusivity is much harder to overthrow because it is an administrative procedure enforced by the EMA. "Market exclusivity gives companies an unprecedented tool for sealing off markets," he said.

One of the most pressing examples is the case of imatinib (Glivec), the second best selling orphan medicine ever registered in the EU with a total worldwide revenue of €43bn. Novartis markets imatinib in the EU since 2001, for chronic myeloid leukaemia. In 2007, the company also acquired an orphan designation for the same indication with nilotinib (Tasigna). Novartis successfully argued that nilotinib provided a "significant benefit" compared with imatinib in treating chronic myeloid leukaemia. Because the products were deemed "similar," nilotinib impinged on the market exclusivity of imatinib. Under the legislation, however, a company

may consent to a second applicant for a similar product entering the market. Which is exactly what Novartis did: the company gave itself permission to break the market exclusivity of imatinib.

This had major consequences for generic competitors. Although imatinib's market exclusivity for chronic myeloid leukaemia ended in 2011, the EMA refused to authorise a generic application a year later. A generic version of imatinib would infringe the market exclusivity of nilotinib, the EMA argued, which would apply till 2019. Teva, the Israeli company developing the generic, challenged this decision and took the case to the Court of Justice of the European Union. Teva claimed that Novartis had abused the orphan incentives to keep competition at bay for a product that technically was free to copy.

The court dismissed the appeal and ordered that the EMA had interpreted the orphan legislation correctly.[9] When asked for comment, a company spokesperson told us that Novartis "never sought or intended" to acquire overlapping market exclusivities between imatinib and nilotinib. The company said that it voluntarily "granted consent" on multiple generic competitors of imatinib between 2016 and 2018, after compound patent protection of imatinib had expired.

Struggle for reform

The EMA was asked to comment on our findings but stated that "it would not be appropriate to comment on the [European] Commission study before it is published."

Behind closed doors the EMA seems unhappy with the results of the orphan legislation. During an EMA management board meeting in 2017, Bruno Sepodes, then chair of the orphan committee, acknowledged that access to orphan medicines was often challenging and emphasised the need "to fully exploit the legal possibilities . . . to reduce protection periods for orphan medicines that do not meet the criteria over time."[10]

Whether the EMA can effectively battle the misuse without the legislation itself being altered remains to be seen. In 2015, the EMA refused to validate an application for idursulfase-IT, an orphan medicine for the treatment of Hunter syndrome. Though the applicant, Shire (which was recently acquired by Japanese drug maker Takeda) promised that this product would provide a "significant benefit" over existing treatments, the EMA argued that it contained the same active substance as another old orphan medicine, idursulfase (Elaprase). The only notable difference was the method of administration—the newer version is delivered intrathecally, the original intravenously. The older product acquired market exclusivity in 2007 and, according to the Investigative Desk's data, made €4.2bn during its lifecycle.

Shire took the matter to the European General Court, which annulled the EMA decision in 2018.[11] Idursulfase-IT is expected to be authorised in the EU this year or next year. Until this day, no biosimilar of the original idursulfase has entered the European market.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following: LH declares: I am a freelance journalist, but my main client is the pharmaceuticals desk team of The Investigative Desk, a non-profit organisation for investigative journalism. The Investigative Desk is a foundation. Our work is currently financed by the Dutch Journalism Fund (in turn funded by the Dutch government), the Open Society Initiative for Europe (part of Open Society Foundations), the Dutch Cancer Society, the Dutch Fund for In-depth Journalism, EU Journalism Fund, Bath University, and fees for sold articles in different media outlets. In 2019, I spoke at an in-service training by and for hospital pharmacists about high priced medicines, reimbursement, and industry strategies to fend off competition from generic or biosimilar companies. I received €350 for this service, paid for by *Farma Actueel*, a small magazine for pharmacists. In 2019, I was invited to talk at Pfizer Netherlands Medical Day about how an investigative journalist looks at the pharmaceutical industry and to debate on statements about the industry. I could say what I wanted, and I denied payment for this day, but Pfizer compensated me for my travelling expenses (€18.90). At the end of the day, I received a bottle of wine and a cheese. DM: I am a freelance journalist, working for The Investigative Desk and for the Dutch commercial radio station BNR Nieuwsradio. My husband (FJ Borm) is employed as a thoracic oncologist at Leiden University Medical Hospital and is currently a PhD student at NKI-AVL (Netherlands Cancer Institute). His research project is partly funded by Merck Sharp & Dohme and Bristol-Myers Squibb.

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