America's Overspend: How the Pharmaceutical Patent Problem is Fueling High Drug Prices

The American health system is poised to incur $55 billion in excess costs from pharmaceutical companies' strategies to delay competition on three drugs

EXECUTIVE SUMMARY

This analysis of three high-cost drugs for cancer and hepatitis C reveals that anti-competitive strategies by branded pharmaceutical companies are driving excess costs to American payers and patients. Product lifecycle management, whereby branded companies obtain unmerited patents to delay competition, is the primary strategy identified and evaluated by this study. A related strategy is "pay-for-delay": branded companies pay generics to stay off the market, a symptom of underlying unmerited patents and misaligned incentives in the patent and regulatory systems. The following three multi-billion dollar blockbuster drugs were all found to have questionable – and likely unmerited – patents that are providing excess exclusivity periods.

These unmerited patents and related anti-competitive strategies permit patent holders to delay competition from generic equivalents by decades, which in turn keeps prices artificially high for healthcare payers and taxpayers:

- **Revlimid® (lenalidomide):** Unmerited patents enable a minimum exclusivity period from 2019 through 2028. Payers are projected to spend $45 billion in excess costs for the drug within this period, prior to the first generic product entering the market.

- **Sovaldi® (sofosbuvir):** Unmerited patents will prevent competition from now through 2034, when final patents held by Gilead Sciences expire on the drug. Payers are projected to incur $10 billion in excess costs.

- **Gleevec® (imatinib):** In the one-year period from 2015-16, approximately $700 million dollars in excess costs were passed onto payers as a result of a pay-for-delay deal cut by Novartis to a generic company in exchange for delaying the entry of generic imatinib.

This analysis found that the American health care system is poised to incur $55 billion in excess costs in the next 15 years on these three drugs alone due to unmerited patents blocking generic competition.

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INTRODUCTION

One in five American households reported not being able to fill a prescription in the last year due to the high costs of medicines.[1] States are being forced to ration or deny lifesaving medicines to patients, with newer specialty medicines causing budgets to crumble under the weight of skyrocketing prices.[2] The problem is getting worse: since 2008, the cost index for branded drug prices has nearly tripled,[3] and by 2025 prescription drug spending nationally is poised to double.[4] This trend is putting American patients and the sustainability of public payers at risk.

With 70% of American voters across the political spectrum identifying prescription drug pricing as a critical problem,[5] the need for solutions has gained national prominence. Despite the range of solutions being discussed at the state and national level, meaningful price reductions will not be possible without accelerated and increased competition. A vibrant generic drug market with two or more suppliers is the only type of healthy market that consistently and substantially lowers prescription drug prices by more than half.[6] **The lack of effective competition in the prescription drug market is due to monopolies that branded companies hold for decades with over-patenting and pay-for-delay strategies.**

The market for pharmaceuticals in the U.S. is inefficient and incentives in the drug development system are not aligned with desired outcomes. The continual extensions of market exclusivities enabled by a combination of out-of-date legislation and the range of tactics used by branded companies to delay competition have created an unbalanced marketplace. This paper examines the underlying patent portfolios and market behavior of three of the most expensive and widely used drugs in America in order to understand whether and how unmerited patents and related strategies are delaying generic competition and driving **overspend** on lifesaving medicines.

Overspend
The difference between the cost of a branded drug and its generic equivalent over the time period in which an unmerited patent was identified as preventing entry of a generic product.

METHODOLOGY

Drug Prioritization

To arrive at the highest-cost and most widely used small molecule prescription medicines in the U.S., this analysis compiled a list of all drugs that ranked on four different lists:

1) The top 20 drugs in overall spending in the U.S. in 2015[7]
2) The top 20 drugs in Medicare Part D spending in 2015[8]
3) The top 20 drugs in Medicaid spending in 2015[8]
4) The 64 unique drugs that met the criteria of being both reimbursed at $600 or more for a one-month prescription and had total annual gross reimbursement of more than $72 million dollars in 2015[9]

Twenty drugs appeared on three or four of these lists, or were on the list of 64 noted above and at least one other list. All biologics and injectables (insulin, monoclonal antibodies,

etc.) were excluded, resulting in a shortlist of twelve small molecule products. Given the in-depth nature of the patent review process (described below), this preliminary analysis focuses on three drugs. These drugs were selected as those that are the most widely reported to be causing significant financial strain to patients and purchasers[10-12] and ensuring that the analysis included different patent holder companies.

Shortlist of top 12 high cost small molecule drugs

Drug	Disease	Patent Holder
Abilify®	Bipolar disorder	BMS
Atripla®	HIV	Gilead
Gleevec®	**Oncology**	**Novartis**
Harvoni®	Hepatitis C	Gilead
Invega®	Antipsychotic	Johnson & Johnson
Latuda®	Schizophrenia	Sunovion Pharma
Lyrica®	Neuropathic pain	Pfizer
Revlimid®	**Blood related disorders**	**Celgene**
Sovaldi®	**Hepatitis C**	**Gilead**
Stribild®	HIV	Gilead
Tecfidera®	Multiple sclerosis	Biogen
Truvada®	HIV	Gilead

Patent Analysis[i]

Both patent landscaping and validity analyses were conducted on the three drugs in order to a) map all the key patents on each drug, b) identify the patent expiration dates and related FDA marketing exclusivity periods, and c) evaluate the validity of each patent.

Each patent and the scope of its protection was reviewed, including if the patent would be a barrier to competitors in order to operate freely and verifying if patents are listed on the U.S. FDA Orange Book. These are deemed the most important patents that a branded company would assert if a generic entrant were to file an Abbreviated New Drug Application (ANDA)[ii] to enter the market with a generic version. While the listed patents on the Orange Book are typically considered the higher value patents, other non-listed patents can also pose problems for potential generic entrants, and therefore all potential patent blocks to generic competition were assessed.

Finally, "prior art" or evidence searches and technical expert reviews were conducted to assess the validity of the patent for novelty and obviousness, the key measures of whether a patent is merited or not. Experience shows that the legal obviousness inquiry is often diluted in patent examination and court review of drug patents. For this reason, this scientific and legal evaluation focuses on a thorough application of the legal standard of obviousness.

Patent searches were conducted up until September 15th 2017.[iii]

Cost Modeling

For each drug, a cost model was built to quantify the financial impact of unmerited patents or pay-for-delay settlements blocking entry of generic products into the market over time. The models used a variety of real-world annualized market-based assumptions to assess the financial impact –excess costs incurred – that resulted from comparing *status-quo* market conditions (current expiry of patents on a drug) to those that reflected earlier entry of generic

[i] Detailed methods and results available upon request

[ii] The standard regulatory documentation and pathway by which generic products demonstrate equivalency to a branded product are reviewed and approved by the FDA

[iii] As patent applications in the United States are usually published after eighteen months, patent applications filed less than eighteen months before the search date were not captured. Also patent applications that were withdrawn before publication cannot be picked up in any search.

products. The model accounts for ANDA filing eligibility and assumes that the accelerated entry of a generic product to the marketplace is consistent with standard timelines for ANDA review and approval.

Other key variables considered annually in the analysis included:

- The total size of the patient pool and the number of patients coming onto treatment each year.
- The market share of the product being evaluated relative to the competitor landscape.
- Pricing and payer discounts and market dynamics for both branded and generic drug equivalents.
- The share of patients that can potentially benefit from generic products.

All models were created with clinical assumptions intended to reflect how the generic version of each drug would be used in the real-world setting. This included considerations for pairing generic equivalents with other drugs that may not have otherwise been possible given unmerited patents restricting such opportunities.

CASE STUDY ANALYSIS

Revlimid®

Developed by U.S. biopharmaceutical company Celgene, Revlimid® was first approved in the U.S. in 2006 to treat multiple myeloma. It has since been approved for multiple other hematology cancers and indications. It has been the main driver of Celgene's revenue growth in the past decade, netting the company $43 billion dollars to date, and comprising two thirds of the company's total annual revenue. Priced at over $125,000 per year of treatment, it ranks among the most expensive medicines available on the market. Moreover, Celgene has raised the price of the drug by more than 50% since 2012: today, a single 10mg tablet costs about $600. It is not just the list price of the drug that is high.[13] A recent study revealed that the median out-of-pocket cost for a Medicare patient on Revlimid® was $11,500 per year, the highest among other high-cost specialty drugs.[14]

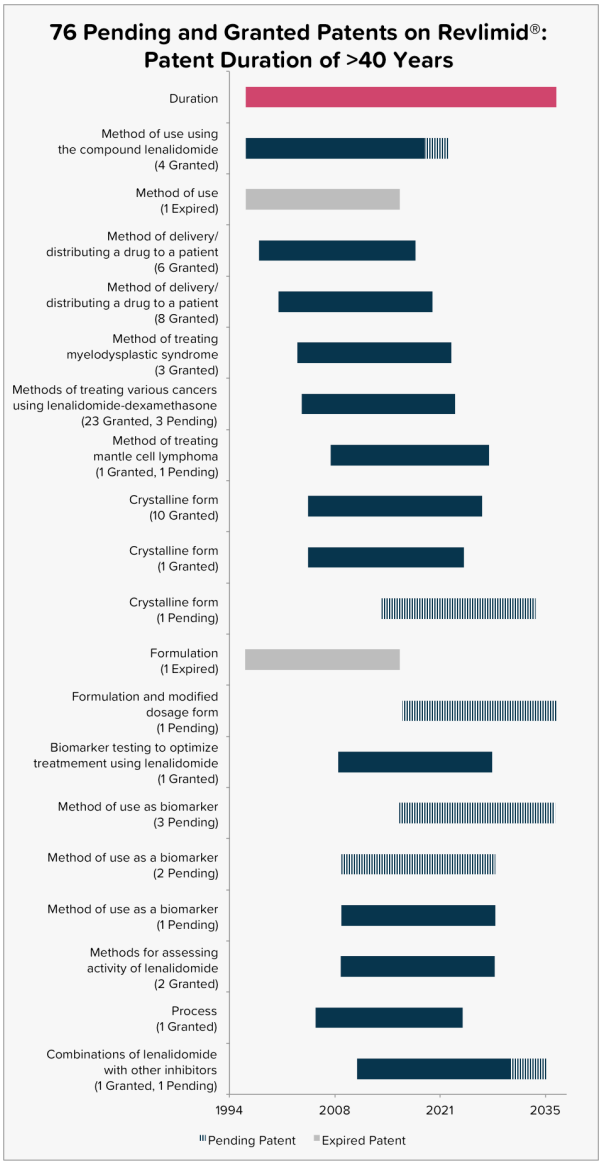
Patent Analysis

The compound used for Revlimid® is known as lenalidomide, a derivative of an older parent compound thalidomide, first marketed in 1957 as a sedative or hypnotic. Later, in the 1960s, it became public knowledge that this compound and its derivatives possessed anti-inflammatory properties. Research done by actors other than Celgene in the early 1990s showed that it could also be used to kill tumor cells.

The patent analysis identified a total of 76 granted patents and patent applications for Revlimid® (lenalidomide) as held by Celgene and related companies that have been acquired.[iv] In addition, there are 29 abandoned patent applications, making a total of 105. In total, including the pending patent applications, the combined patent protection for these drugs is potentially set to expire at the end of 2036, giving Celgene's Revlimid® patent portfolio a lifespan of at least 40 years.

[iv] For example, Signal Pharmaceuticals, Inc.

Revlimid® Patent Landscape



These 105 patents cover the various hematology cancers and indications for which Revlimid® has been approved. The landscape for Revlimid® comprises the following categories of patents which cover the various indications it has been approved for: methods of use and treatment, including biomarkers, crystalline forms, formulations, devices for assisting patients with filling their prescriptions and controlling distribution of lenalidomide, combination with other inhibitors, and processes for manufacturing lenalidomide. Typically, all these types of patents would be classified as secondary patents. Of the 66 currently granted patents on Revlimid®, 27 are listed on the U.S FDA Orange Book.

This expert review showed that in light of the prior art available in the field, there is a substantial body of evidence to suggest that all of these granted patents and pending patent applications protecting Revlimid® would be unmerited if the legal standards of novelty and obviousness were applied. Overall, this assessment concludes that Celgene developed a thicket of patents as a defensive strategy to protect Revlimid® in order to maximize its monopoly hold as long as possible and block generic competition. Indeed, generic versions should be able to enter the market at least in October 2019.[v]

This assessment is supported by the settlement between Celgene and Natco, who challenged the very first patent on Revlimid®. Indeed, numerous other generic companies are currently in litigation with Celegene over its various patents. This suggests Celegene's entire patent portfolio, from the first patent listed on the Orange Book to the latest pending ones for Revlimid®, is built on unmerited patents.

Cost Analysis

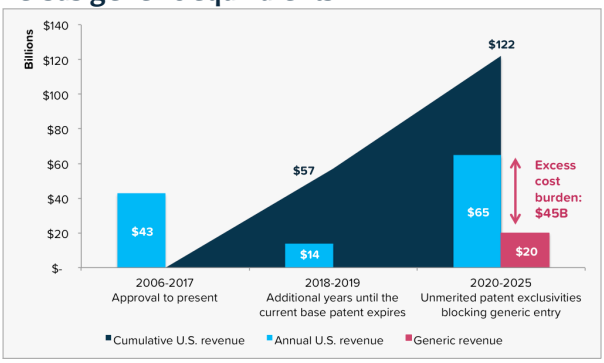
Excess costs associated with unmerited patents on Revlimid® were analyzed over a five-year period: from October 2019 when the main

[v] While out of the scope of this paper, though consistent with the over-patenting strategies used by Celgene to thwart generic competition, the company has also been accused of REMS abuses: intentional efforts by branded companies to restrict generic companies from gaining access to product samples in order to conduct bioequivalence studies. These so-called REMS abuses have been cited as a major tactic by branded companies to delay the introduction of generic products to the market.

patent expires through the end of 2025 when the first "unrestricted" generic product could enter the market. This is the outcome of the deal referenced above wherein Celgene made with generic company Natco in exchange for them dropping patent challenges against Celgene. The deal gave Natco unrestricted or volume-unlimited generic product sales beginning in January 2026, about a year before the expiration of Celgene's last granted patent (although there are many other pending applications that could extend exclusivities to 2036). Conservatively, the cost analysis only examined the period until the first generic product could enter the market (2025).

Based on the historical and projected revenue of Revlimid®, Celgene is projected to earn $65 billion dollars between 2020 and 2025[vi]. To calculate excess costs, the difference in overall costs between purchasing branded versus generic products during this time period was assessed using conservative estimates for the brand-to-generic discount of just 20% in 2020 and increasing to 80% in 2025. **The analysis found that this overspend on Revlimid® attributed to the unmerited patents is estimated to be $45 billion dollars**.

Summary of U.S. Revlimid® revenue and the estimated excess costs for branded Revlimid® versus generic equivalents



Sovaldi®

Sovaldi® (sofosbuvir) was purchased by Gilead Sciences in 2011 and received FDA approval in December 2013 to treat chronic hepatitis C. It was the first of a new generation of direct-acting antiviral drugs that, in contrast to earlier treatments, had greater than a 90% cure rate, lower risks of side effects, and a shorter treatment course. The introduction of Sovaldi® and other therapies that followed – using sofosbuvir as a backbone in combination therapy – have raised the realistic prospects of eliminating hepatitis C in the U.S. and worldwide. However the price of Sovaldi® and its combination therapies remains the major impediment to that possibility.

Sovaldi® launched at a list price of $84,000 for a standard twelve-week treatment course, or about $1,000 a pill. The net prices actually paid for sofosbuvir-based drugs by various public and private payers after rebates and discounts are inevitably less than the list prices. At the most recent average net price of $45,000 per patient for all sofosbuvir-based products in the U.S.,[15] it would cost $135 billion dollars to treat the estimated three million people with chronic hepatitis C in the U.S. – over one third of total annual spending on *all* prescription drugs in the

[vi] This is *in addition* to the $57 billion dollars Celgene is projected to earn while the main patent is still in place (total revenue of $122 billion dollars).

U.S. The high prices of the sofosbuvir-based treatment are the primary barrier preventing more widespread access to treatment.

Of Americans who have been diagnosed with chronic hepatitis C, over 85% are not getting access to treatment this year.[16]

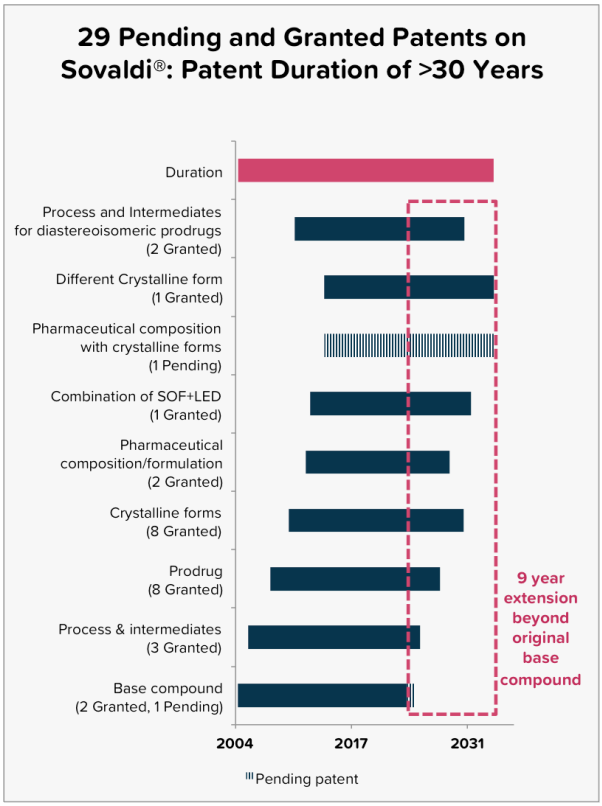
Patent Analysis

The patent analysis identified 27 granted patents, 2 patent applications, and 16 abandoned patent applications[vii] for a total of 45 patents filed by Gilead protecting Sovaldi® (sofosbuvir).[viii]

Out of the total of 29 granted patents and patent applications, 26 are secondary patents covering prodrugs of the basic compound patent, process patents, formulations, crystalline forms, and methods for treating hepatitis C using Sovaldi®. The remaining three granted patents and patent applications related to the basic compound that protects the active ingredient found in Sovaldi®. Of the 27 granted patents, nine are listed on the U.S FDA Orange Book.

In total, the combined patent protection of these patents is over 30 years. Based on Gilead's patent filing strategies on its other drugs, experts anticipate the company will continue to add additional patents in order to extend the monopoly position.[17]

Patent landscape for Sovaldi®



The expert assessments showed that in light of the prior art available in the field, the patents are likely unmerited. With respect to the base compound, the existing knowledge in the field of nucleosides for antiviral use laid the path for a single change that was made to create sofosbuvir. As such, this should raise the question of obviousness. Similarly, the prior knowledge and techniques for the development of the prodrug, formulations, and crystalline forms of sofosbuvir have all been mapped out in earlier research and raise questions around the novelty and obvious nature of these patents.

Overall, this assessment concludes that the granted patents and patent applications for Sovaldi® are unmerited and are unnecessarily blocking competition.

Cost Analysis

[vii] Applications that have been abandoned can be re-filed as continuation applications and which may ultimately get granted. For the purpose of this study, any abandoned applications that were re-filed were captured in the granted patents or patent applications that are under examination.

[viii] The patents are officially held by Gilead Pharmasset LLC. Gilead acquired Pharmasset in November 2011, acquiring their entire sofosbuvir patent portfolio.

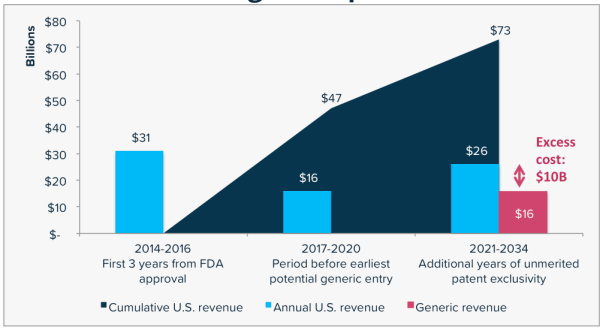
Based on the historical and projected revenue of Sovaldi® and the Sovaldi®-based combination drugs, it is estimated that Gilead will earn a total of $73 billion dollars in revenue in the U.S. on these hepatitis C drugs from 2014 through 2034. Within that timeframe, the revenue was separated into three different time periods:

- **2014-2016:** The three-year period following FDA approval in which a total of $31 billion dollars in revenue was made on these products in the U.S.
- **2017-2020:** Four-year period with projected *additional* $16 billion dollars. in U.S. revenue. This timeframe represents the period in which a combination of exclusivities, patents, and legal stays effectively prevent generics from entering the market.
- **2021-2034:** An *additional* $26 billion dollars is projected to be made by Gilead in the U.S. on the Sovaldi®-based hepatitis C drugs during this fourteen year period in which a host of identified unmerited patents could prevent generic product entry.

To estimate the total costs of generic products the model used the time period from 2021 to 2034. This represents the earliest period in which a generic product could be introduced through the end of the last exclusivity period identified. This analysis was based on the assumption that the availability of a generic sofosbuvir would open up multiple combination drug possibilities that are not currently available. Principally, the analysis modeled the generic costs based on the use of a generic sofosbuvir and daclatasvir product that would be priced 15-20% below the average market price of branded products and utilized in the minimum of one-third and maximum of two-thirds of patients each year. From this the total costs of generic sofosbuvir combination products during this time period were estimated to be $16 billion dollars.

The excess costs linked to unmerited patents during this time period is the difference between the projected costs of the branded and generic products overall costs between purchasing branded versus generic products during this time period. The analysis estimates this **overspend on Sovaldi® attributed to the unmerited patents to be $10 billion dollars.**

Summary of U.S. revenue from Sovaldi®-based combination drugs and estimated excess costs for branded versus generic products



Gleevec®

The cancer drug Gleevec®(imatinib) was developed by Novartis and received U.S. FDA approval in May 2001 to treat chronic myeloid leukemia. It went on to become a major blockbuster for the company generating over $40 billion in global revenue and $15 billion in the U.S. during its lifetime as a leading branded product for Novartis until early-2016. In 2001, when Gleevec® first became commercially available, the price was $26,400 per year; since then the price has more than quadrupled and now costs $108,000 per year.[18]

Sun Pharmaceuticals, an FDA-approved generic

manufacturer, was the first to file an ANDA with the FDA for approval of a generic imatinib, choosing what is known as "paragraph IV certification," in which Sun asserted that it was not infringing on the patents held by Novartis because they deem them invalid. This type of patent challenge by a generic company is a regular practice in the U.S.

With its base patent set to expire on Gleevec® in July 2015 and the paragraph IV challenge filed by Sun, Novartis had two choices. Either risk pursuing the full course of litigation with Sun over the legitimacy of its secondary patents that they could likely lose — or try to cut a deal with Sun. Novartis elected the latter option and struck a pay-for-delay deal with Sun that enabled Novartis to extend their commercial exclusivity on Gleevec® for six months (from August 2015 to January 2016). Novartis also continued a duopoly market with a similarly high-priced generic drug made by Sun during the generic company's 6-month exclusivity period (February to August 2016).

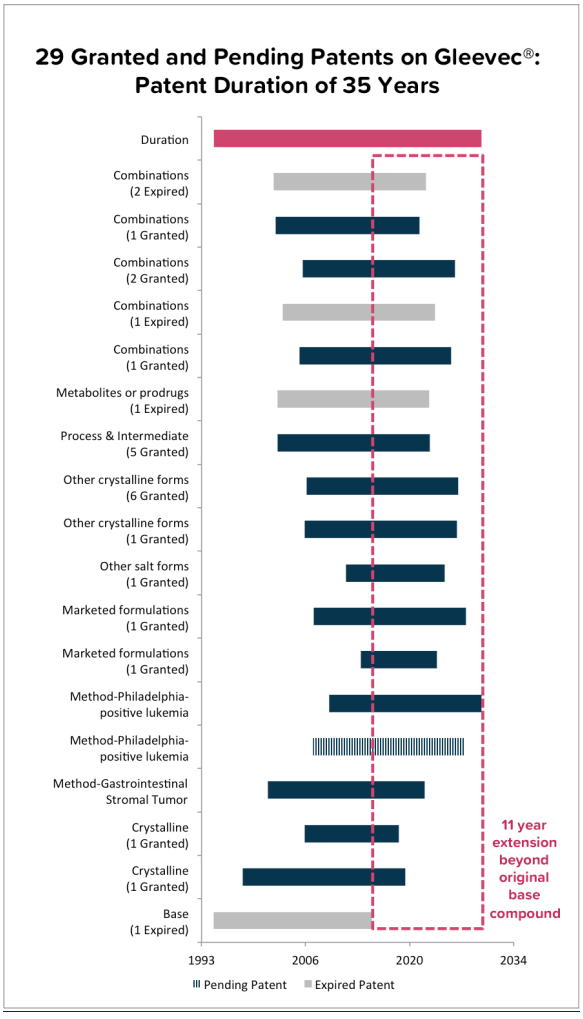
Patent Analysis

The patent analysis identified 23 granted patents, five expired patents (including the base compound), one pending patent application, and 44 applications had been abandoned[ix] for a total of 73 patents.

Eight of the 23 granted patents are currently listed on the U.S FDA Orange Book. The patent covering the base compound was previously listed but has now been removed as it has now expired.

Out of the total of 29 granted patents and patent applications found for Gleevec®, 28 were secondary patents covering crystalline forms, salt forms, methods of treatment, formulations, prodrugs, processes, dosage forms, and combinations with other drugs. The last of these secondary patents is currently set to expire in 2029. That is an additional 11 years of patent protection over the expiry date of the base patent.

Patent landscape for Gleevec®



A review of the current non-expired granted patents and pending applications found ample evidence to suggest that these patents are all

[ix] Applications that have been abandoned can be re-filed as continuation applications and which may ultimately get granted. For the purpose of this study, any abandoned applications that were re-filed were captured in the granted patents or patent applications that are under examination.

unmerited on the grounds of novelty or obviousness. These are later, secondary patents that are being filed to simply extend monopoly protection.

Cost Analysis

Recognizing the circumstances of the Novartis and Sun settlement, this analysis examined the actual costs of this deal to payers and the broader healthcare system. Broadly, the excess costs to payers are two-fold:

1. The six-month pay-for-delay extension of Gleevec® exclusivity beyond the patent expiration, from August 2015 through January 2016
2. The artificially high generic price of imatinib in the following six-month period, from February through July 2016. While the first outcome benefitted Novartis and the second benefitted Sun, the sum total of both was borne by the payers in the healthcare system

Records shows that Novartis earned about $1.3 billion dollars in net Gleevec® sales in the U.S. for the six months — from August 2015 through January 2016 — during which they paid Sun to delay the introduction of their generic product. And in the following six-month period from February to July 2016 data from IMS suggests that Sun Pharma made approximately $500 million dollars. Together these tactics resulted in a total of nearly $1.8 billion dollars in Gleevec®/imitinab revenue for Novartis and Sun, all earned *after* the Gleevec® patent should have expired and a well-functioning generic market should have emerged.

For comparison, a model was developed to reflect the costs for generic imatinib had there not been the pay-for-delay deal that extended Gleevec®'s exclusivity and the artificially high generic price set by Sun during the subsequent 180-day exclusivity period. In this hypothetical scenario there would have been generic entry by Sun in August 2015 (instead of February 2016) and they would have had a 180-day exclusive marketing period.

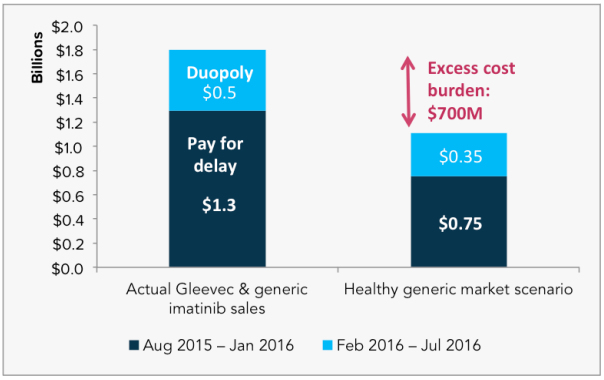
The following key assumptions for an analysis of a healthy generic market were used:

- Sun would have launched their generic at a 30% discount to Gleevec® as they initially indicated — and that Novartis would have their authorized generic[x] on the market beginning in August 2015
- The likely outcome of this would have been the price of the generics would have gone from an initial 30% discount to a 50% discount by the end of the first six-month exclusivity period
- In February 2016, this evaluation assumes that three or more other generic suppliers would have entered the market and, as is typical of healthy generic marketplace dynamics with multiple competitors, the prices rapidly decline
- As has occurred with other high-priced products moving to generics, this analysis assumes the additional competition in the second six-month period would have resulted in further discounts from 70 to 80% by July 2016

[x] The term **authorized generic** refers to prescription drugs that are produced by brand companies and marketed as generics under private label. They compete with standard generic products approved by the FDA and are marketed to consumers during and after the 180-day exclusivity period awarded to the first-to-file generic product.

Taken together the analysis comparing what actually occurred in the marketplace with what would have likely occurred in a healthy generic marketplace had there not been the pay-for-delay settlement shows there was an **excess cost burden of nearly $700 million dollars.** Novartis and Sun profited by approximately $1.8 billion dollars in total from this pay-for-delay settlement arrangement, this analysis shows that the total cost of those same medicines in a well-functioning generic marketplace would have cost about $1.1 billion dollars.

Summary of excess costs from a pay-for-delay deal for Gleevec®



THE WAY FORWARD

This initial analysis found that the American healthcare payers and patients are poised to overspend $55 billion on just three cancer and hepatitis C medicines in the next 15 years. Unmerited patents and related strategies are the key driver of these excess costs as branded companies work to create competition-free zones[xi] by blocking generic entrants to the market.

Key findings include:

- Celgene has filed over 100 patents on its blockbuster anti-cancer drug Revlimid®, and its patenting strategies are likely to extend its monopoly for two more decades. In total, Celgene's patenting strategies will provide it with 40 years of market control, and its unmerited patents will cost payer and taxpayers $45 billion more than if lower-cost generic alternatives were appropriately allowed to enter the market.
- Gilead Sciences has filed 29 patents currently set to run to 2034. Unmerited patents between 2021-2034 are poised to cause $10 billion in overspend on Sovaldi® for payers and patients from these if generic equivalents were unlocked were entering the market.
- Novartis executed a pay-for-delay deal to stall the entry of a generic Gleevec® product by six months. This analysis found the just six-month extension of Gleevec® exclusivity cost the country's healthcare payers an excess of $700 million dollars.

With prescription drug spending poised to double and Americans across the political spectrum demanding change, more research is needed to evaluate the scope of this problem in order to shape effective solutions. Next steps include:

- A comprehensive evaluation of the most expensive and widely used small-molecule medicines in America today.
- An impact analysis on specific payers: which state, federal and private payers are affected by over-patenting, regulatory abuses, and other anti-competitive tactics.
- Assessments of which specific diseases and/or patient populations are most impacted or disproportionately affected by the high cost of prescription drugs tied to unmerited patents.
- An examination of transaction costs: how much could the U.S. save domestically if these unmerited patents were curbed at the patent examination stage instead of after-the-fact through patent challenges (*ex ante* vs. *ex post*).

Failures and inefficiencies in the medicines market are resulting in excess costs on prescription drug spending and need correction. This preliminary data-driven analysis offers some insight into the overspend for use by policymakers and others searching for evidence to inform solutions for change.

[xi] This term was coined by Robin Feldman, Director of the Institute for Innovation Law at the University of California Hastings College of the Law: http://innovation.uchastings.edu/news/professor-robin-feldman-testifies-before-house-judiciary-subcommittee-on-soaring-prices-and-shortages-for-addiction-medicine/

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