Journey of Generic Imatinib: A Case Study in Oncology Drug Pricing

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In February 2016, a generic version of imatinib (Gleevec), the groundbreaking tyrosine kinase inhibitor, was made available in the United States. Imatinib has ushered in a new era of targeted oncology drug development, but has also been credited with creating a new era of drug pricing. At its introduction in 2001, the list price of imatinib was an unprecedented $26,400/year, but this was justified by the novelty of its molecular mechanism and the relative rarity of its approved indications. At the time of generic entry, the list price had risen to $120,000/year (Fig 1). Although approved for only a handful of rare diseases, including chronic myelogenous leukemia and GI stromal tumor (GIST), imatinib generated $4.7 billion in 2015 alone. These high drug prices have been linked to nonadherence among patients. The arrival of generic imatinib, therefore, was widely anticipated by patients and physicians.

Here, we review how various market strategies slowed the entry of generic imatinib in the United States compared with other countries—it was available as early as 2013 in Canada—and how the transition from branded to generic imatinib by US patients continues to face hurdles. We conclude with recommendations about how to improve the availability of and access to generic medications as part of a broader strategy for promoting optimal delivery of patient care.

A Timeline Leading Up to the First Availability of Generic Imatinib

The initial US patent on imatinib was set to expire in May 2013; however, after the drug’s 2001 US Food and Drug Administration (FDA) approval, Novartis filed for a patent term restoration, which grants drug manufacturers a patent extension for a period of time equal to the length of time the drug is under FDA review plus one half its clinical trial testing period (to a maximum of 14 years). Imatinib’s patent also received a pediatric exclusivity extension, which grants an additional 6 months of protection to pharmaceutical companies that respond to an FDA request to conduct a clinical trial in pediatric patients. As a result of the patent term restoration (586 days) and pediatric exclusivity (180 days), imatinib’s patent was extended from May 2013 to July 2015.

In addition, Novartis sought numerous additional patents on imatinib. Such so-called secondary patents are meant to protect incremental changes that can be useful—for example, a new formulation that allows once-daily versus twice-daily dosing—but often are sought for minor alterations to a drug or its manufacturing process that do not provide effectiveness or safety advantages over the original drug product. The US Patent and Trademark Office (USPTO) approves patents that cover nonobvious changes over prior versions, but has a low bar for applying this criterion. Secondary patents have become widely used by brand-name manufacturers to extend the life cycle of patented products; branded manufacturers in 2007 listed with the FDA an average of 10 patents per drug compared with an average of two patents per drug in the previous decade. In this case, secondary patents on imatinib that covered a different...
formulation of the active ingredient further extended its potential market exclusivity from July 2015 to November 2019 without offering additional clinical benefits.

Secondary patents are more likely than active ingredient patents to be challenged by generic manufacturers and overturned in court; however, brand-name and generic manufacturers frequently settle such disputes in so-called pay-for-delay deals. The US Supreme Court has recently found that such settlements are open to scrutiny when they involve cash transfers, but other agreements are not subject to review. In the case of imatinib, generic drug manufacturer Sun Pharma (Mumbai, India) challenged the validity of the secondary patents and, in May 2014, Novartis and Sun Pharma settled their litigation, with Novartis agreeing to allow Sun Pharma to launch its generic version in February 2016, with other terms of the settlement undisclosed.

Some might view this as a success of patent law, as Novartis was permitted to file for patents that the company argued were substantive, and a generic manufacturer was granted earlier access. An alternative viewpoint is that Novartis won an additional 9 months of exclusivity for its branded product by using questionable patents, which allowed it to earn more than half a billion dollars during that time.

Suboptimal Use of Generic Imatinib After Approval

Even with generic imatinib now available in the United States, a variety of factors may delay the establishment of lower drug costs. The first generic manufacturer to market is granted 180 days of generic market exclusivity. This initial generic–branded duopoly does not lead to major price reductions. In the case of imatinib, Sun Pharma priced its generic product 30% below brand-name price. By comparison, in Canada, generic imatinib is sold for approximately 82% below brand-name price. More drastic price decreases will likely not be seen until more generics enter the market after the exclusivity period.

Another factor is competition from second-generation tyrosine kinase inhibitors. In addition to imatinib, Novartis has developed nilotinib (Tasigna), which was approved in 2008 as a first-line treatment of chronic myelogenous leukemia. It is common practice for pharmaceutical manufacturers to develop separate but related products to their blockbuster drugs and invest heavily in marketing that is intended to shift prescribing to the newer, patent-protected product as market exclusivity on the first drug expires, a practice that is called product hopping. When the proton-pump inhibitor, omeprazole (Prilosec; Proctor & Gamble, Cincinnati, OH), neared the end of its patent protection, AstraZeneca (Cambridge, United Kingdom) began heavily promoting its patented follow-on proton-pump inhibitor, esomeprazole (Nexium), to physicians. Esomeprazole is a purified version of omeprazole with no clear evidence of clinical superiority, yet it became one of the most frequently prescribed drugs in the world. Novartis has launched advertising campaigns to steer oncologists away from imatinib and toward nilotinib, which has an annual list price of $115,000 and is under patent protection until 2026. Nilotinib generated $1.6 billion in sales in 2015, up from $425 million in 2014.

A variety of other challenges remain. There is skepticism among some physicians and patients about the clinical impact of nilotinib compared with imatinib, particularly in terms of long-term safety and efficacy. These factors, along with the cost of the drug, may delay the widespread adoption of nilotinib.

**Fig 1.** Average wholesale price of Gleevec per year at 400 mg per day—typical dosing for chronic myelogenous leukemia maintenance therapy—from 2005 to 2015, according to Redbook data. Prices were adjusted to 2015 USD using the US Department of Labor’s Consumer Price Index.
equivalence of brand-name and generic drugs,\textsuperscript{22,23} which may be reinforced in the case of imatinib by industry-backed non-scientific publications or anecdotal testimonials that cast doubt on the FDA approval process for generic drugs. These can lead to physicians writing dispense-as-written prescriptions that require pharmacists to dispense the brand-name version.\textsuperscript{24,25} When generic versions become available, branded pharmaceutical manufacturers often expand copay assistance programs to patients. By reducing out-of-pocket costs, manufacturers hope to sway patients to remain on the branded form while continuing to profit because most of the cost of oncology drugs is paid by insurance rather than through copays.\textsuperscript{26} The Washington Post reported on a patient taking imatinib who unexpectedly qualified for a Novartis patient assistance program as the generic launch date approached after years of being denied this kind of financial relief.\textsuperscript{1}

Finally, although the imatinib active ingredient patent has expired, Novartis retains a secondary patent on the use of imatinib for the treatment of GIST. Payers are not able to advertise the availability of generic imatinib for GIST treatment until this use patent expires in 2020.

**Recommendations**

Expanding the timely availability and appropriate prescribing of generic medications is a critical and underappreciated policy problem. To achieve this goal, policymakers should advocate for greater scrutiny of drug patent applications by the USPTO. Listing of a patent with the FDA could automatically generate for greater scrutiny of drug patent applications by the USPTO. A new administrative body that reviews patent appeals and postissuance patent challenges to determine whether the patent was appropriately granted.\textsuperscript{27} Raising the cost of patent filings for pharmaceutical companies could also discourage unmeritorious secondary patent listings.

Another approach to prevent unnecessary delays in generic drug availability is to reduce the prevalence of the pay-for-delay litigation settlement deals between generic and branded drug manufacturers. When these deals are completed, they are currently submitted to the Federal Trade Commission but remain protected as confidential commercial information. Instead, the highlights of such deals should be publicly disclosed to allow policymakers and researchers to better understand how they contribute to high drug prices and to guide more thoughtful regulation.

Finally, clinicians can take a more active stance in educating their patients about the safety of generic drugs. To this end, they can use value frameworks released by prominent cancer organizations, including ASCO, to assess the relative clinical and financial value of high-priced therapeutics, such as second-generation tyrosine kinase inhibitors versus newly available generic imatinib.\textsuperscript{28-30}

Although the political discourse around reducing drug spending has focused primarily on strategies to reduce the prices of branded drugs, expanding the timely availability and appropriate prescribing of generic medications can also improve patient outcomes and reduce overall health care spending.\textsuperscript{31}

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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