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PATENT WATCH

Drug patenting in India: looking back and looking forward

Patent protection for drugs in India has been a contentious issue in recent years, with several high-profile denials of patents; for example, for Novartis's anticancer drug imatinib mesylate (Glivec). Much of the debate around pharmaceutical patenting in India has focused on a particular provision— Section 3(d) — of the Indian Patent Act, which was introduced in 2005 as part of India's implementation of the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) in 2005. It has been argued that 3(d) makes it difficult to obtain patents for new drugs in India (*Health Affairs* **33**: 1567–1575; 2014, and Special 301 Report; 2015 (Further Information)), which has led to numerous calls to overturn or rethink this provision. Here, however, we argue that the attention paid to Section 3(d) may be misleading and that another element of India's TRIPS implementation may be more relevant to the current pharmaceutical patenting landscape in India.

TRIPS, which entered into effect in 1995, required countries to grant pharmaceutical product patents. Prior to this time few developing countries did so. In complying with TRIPS, India took steps aimed to ameliorate the feared effects of pharmaceutical patenting on access to medicines, such as the inclusion of Section 3(d), which aims to curb the granting of patents to new forms, compositions, and uses of existing substances — so-called 'secondary patents'. Secondary patents are legally more vulnerable, not only in India but globally. For example, in the USA most secondary patents are overturned when litigated to completion (*Science* **339**: 1386–1387; 2013). Indeed in the case of Glivec, the secondary patent was the subject of a US patent challenge (*Science* **337**: 414–415; 2012).

While 3(d) has attracted considerable attention, another, aspect of India's TRIPS implementation was to disallow any patents with priority years (year of first global filing) before 1995. During the TRIPS negotiations, pharmaceutical companies lobbied to make patent protection on pre-1995 molecules mandatory, arguing that not doing so would substantially delay the commercial benefits from TRIPS (*Patent World* **75**: 29–33; 1995). These attempts failed.

How important is the 1995 cut-off date? Assuming that the earliest patent for a drug is its compound patent, the majority of the 430 drugs with patents approved by the US Food and Drug Administration (FDA) between 1995 and 2013 had their first patent filing dates before 1995 (FIG. 1, top panel). Even among drugs approved since 2010,, nearly a quarter (23.7%) had their first patents filed before 1995 (FIG. 1, bottom panel).. Of the 23 of these drugs that ranked among the top top 50 drugs by 2012 US sales, 20 had pre-1995 priority dates (Supplementary information S1 (table)). Pre-1995 compound patents are not eligible for protection in India, regardless of Section 3(d) or any other features of the post-2005 Indian pharmaceutical patent system.

Drugs with pre-1995 primary patents must rely on 'weaker' secondary patents as their only form of protection in India, as illustrated by the Glivec case. Novartis' compound patent had a priority date of 1992 (Figure 1), so was not eligible for protection in India. Its application for a secondary patent, covering a crystalline form of the 1992 compound, was rejected in India, on 3(d) and other grounds. As a result Novartis was left with no patent protection at all in India for Glivec.

The outcome in the Glivec case has been interpreted as evidence that 3(d) makes patenting in India too hard—if even a drug like Glivec is unable to obtain patent protection in India, something must be wrong with 3(d). However, the case also illustrates the interaction of 3(d) with the initial policy choice to make pre-1995 molecules ineligible for patents. As 1995 recedes further into the past, drugs with post-1995 compound patents will become typical. As 3(d) mainly focuses on secondary patents, we expect these drugs to obtain patent protection in India. There are exceptions: drugs without compound patents anywhere, and drugs whose compound patents can be construed as derivative and therefore vulnerable to 3(d). However, most new molecular entities have compound patents (*Journal of Health Economics* **31**: 327–339; 2012), and showing that a compound patent is derivative is difficult. Of note, this seems to be the basis of the Indian Patent Office's recent rejection – currently under appeal – of the patent application on sofosbuvir (Sovaldi), Gilead's new Hepatitis C treatment.

The various aspects of TRIPS implementation are interdependent in ways that matter for the future of drug patenting in India. For drugs with pre-1995 compound patents that are not eligible in India, Section 3(d) and other restrictions on secondary patenting may determine whether a drug gets any patent protection at all. For drugs with post-1995 compounds that are likely to be patented in India, the main effects of 3(d), and other restrictions on secondary patents will be on the duration of protection.

The difference between an explanation for rates of pharmaceutical patenting based on 3(d) versus one based on timing is that the effects of the latter are temporary. We anticipate that if 3(d) is implemented as intended, to limit secondary patents, then as 1995 fades further into the past most new molecular entities will get one patent in India, but only one. Whether this is enough protection to balance innovation and access we cannot say. However, 3(d) will not necessarily make India a patent-free zone.

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Figure 1 | Earliest priority year and approval year for patented new molecular entities approved in the USA between 1995 and 2013. This figure plots the priority year (year in which the first patent on a drug had its first global patent application) and year of approval by the US Food and Drug Administration (FDA) for all patented new molecular entities approved by the FDA between 1995 and 2003. The first panel shows priority year versus approval year, with marker size proportional to the number of drugs approved with specific priority and approval year. The second panel shows the share of drug approvals with pre-1995 priority. If we assume the first patent on a drug is its compound patent, drugs with per-1995 priority must rely on secondary patents for protection in India. See Supplementary information S1 (table) for details.

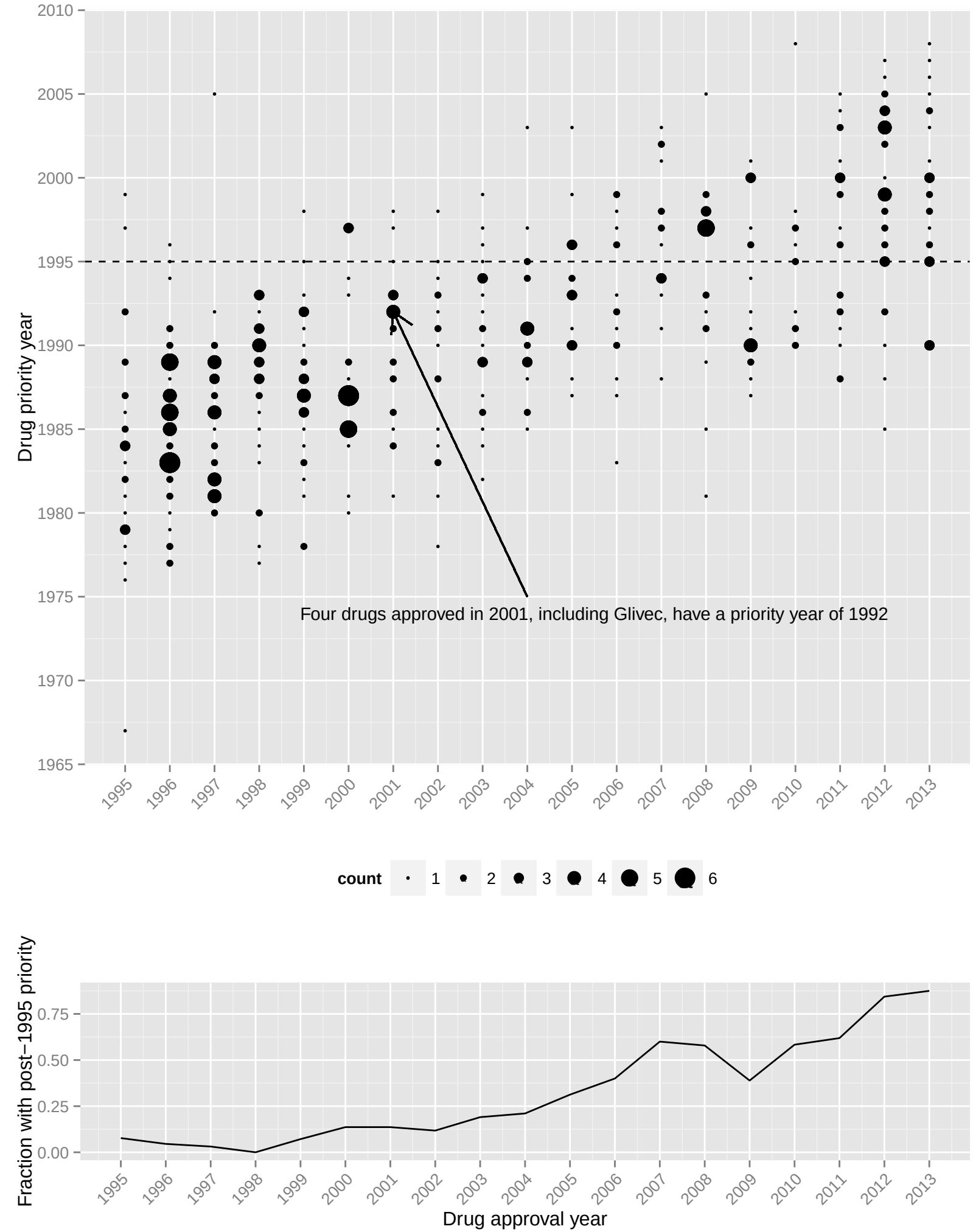
FURTHER INFORMATION

United States Trade Representative. Special 301 Report 2015: https://ustr.gov/sites/default/files/2015-Special-301-Report-FINAL.pdf

SUPPLEMENTARY INFORMATION

See online article: S1 (table)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF


Drug priority year
2010
2005
2000
1995
1990
1985
1980
1975
1970
1965
Four drugs approved in 2001, including Glivec, have a priority year of 1992
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
count
1
2
3
4
5
6
Fraction with post−1995 priority
0.75
0.50
0.25
0.00
Drug approval year

Supplementary Table
Priority and approval year of drugs approved 1995-2012 that were among the top 50 selling drugs in 2012

Sales Rank	*Product*	*Drug approval year*	*Priority year of first patent*
2	Abilify	2002	1978
3	Crestor	2003	1991
5	Cymbalta	2004	1986
9	Copaxone	1996	1994
11	Singulair	1998	1990
13	Plavix	1997	1982
17	Januvia	2006	1996
19	Lantus	2000	1988
23	Diovan	1996	1990
24	Lyrica	2004	1990
25	Lipitor	1996	1986
26	Celebrex	1998	1993
28	Gleevec	2001	1992
29	Namenda	2003	1989
30	Actos	1999	1978
33	Vyvanse	2007	2002
35	Seroquel	1997	1986
36	Zetia	2002	1993
39	Incivek	2011	2000
45	Novolog	2000	1985
48	Alimta	2004	1989
49	Eloxatin	2002	1992
50	Levemir	2005	1993

Notes:
Sales data from http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012

Shading indicates pre-1995 priority

Supplementary Information

Constructing a list of all new molecular entity (NME) drug approvals between 1995 and 2013

We began with the April 2014 version of the U.S. Food and Drug Administration's "Drugs@FDA" database [1]. Using APPLICATION.TXT we determined which applications were new drug applications (appltype=N) and which where for new molecular entities (chemical_type=1). Using REGACTIONDATE.TXT we determined the first approval year for each new drug application. Using PRODUCT.TXT we determined the drug name for the first product (productno=1) associated with each new drug application. We began our analysis with the 486 new molecular entities, hereafter "drugs," approved between 1995 and 2013.

Constructing patent information for each drug

For each of these drugs we then obtained data from the FDA's Orange Book on all associated patents. Because some of the patents on earlier drugs will have expired, and thus no longer be recorded in the current Orange Book, we relied on a dataset of all patents listed in the Orange Book from 1985-2012 [2]. Since our sample extends to 2013 drug approvals, we supplemented this with information from the October 2014 Electronic Version of the Orange Book [3]. We dropped from this set one patent (1712251, on "Manufacture of rolled-steel members") which appears to have been an Orange Book listing mistake.

There were 1776 distinct patents associated with these drugs. Some of the drugs (56) did not have any listed patents. Our analysis uses the 430 drugs with at least one patent.

Determining the earliest priority filing date for each drug

We determined the priority date for each of the 1776 patents [4] using information from the Derwent World Patents Index [5]. For three patents which Derwent was missing information, we used information from the U.S. Patent and Trademark Office instead [6].

Drugs can have multiple patents. These typically include patents on the base molecule, on alternative structural forms of the molecule (e.g. salts, esters, enantiomers, polymorphs), on compositions and formulations, and on uses. We are interested in the priority dates for the compound patents, typically the strongest patents, as discussed in the paper. We did not code each patent to determine if it is a compound patent or not, but rather assumed that the patent with the earliest priority date is a given drug's compound patent [7].

Figure One relates a drug's earliest priority year across all of its patents (which we can think of as the drug's priority year) to its approval year, and shows what share of drugs have priority years before 1995 [8].

Determining which drugs in our sample acheived high sales

Using a list of the top 200 drugs by U.S. sales compiled by *Pharmacy Times* [9], we determined which of the drugs in our sample were among the top 50 in sales in 2012 [10]. The Supplementary Table lists these drugs, along with their priority and approval years.

[1] http://www.fda.gov/Drugs/InformationOnDrugs/ucm079750.htm

[2] Hemphill and Sampat, 2013. "Archival Orange Book Patent Data." Available from authors, on request.

[3] http://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM163762.zip

[4] In some cases patents have multiple priority applications. In such cases we use the earliest priority year.

[5] http://thomsonreuters.com/en/products-services/intellectual-property/patent-research-and-analysis/derwent-world-patents-index.html

[6] http://patft.uspto.gov/netahtml/PTO/srchnum.htm. The patents for which we used Patent Office information instead of Derwent are 8529882, 7820671, and 7668730.

[7] For a set of new molecular entities with first generic entry in the U.S. between 2000 and 2010 (see Hemphill, C. Scott, and Bhaven N. Sampat, "Evergreening, patent challenges, and effective market life in pharmaceuticals," *Journal of Health Economics* 31.2, 2012: 327-339) that had a compound patent, we calculated that the priority year of the compound patent was the earliest priority year (across all patents on the drug) 95 percent of the time.

[8] We assume that patents with priority dates before 1995 are ineligible in India. While this appears to be the conventional view, some experts suggest that applications filed in India after 1995 but with priority dates of 1994 may be eligible. See e.g. http://www.i-mak.org/i-mak-blog-updates/2007/10/3/pre-95-drugs-are-not-patentable-in-india-or-are-they.html and http://spicyip.com/2010/07/prioritising-pharmaceutical-patents-in.html. As a practical matter there are very few granted Indian pharmaceutical patents with priority dates before 1995 http://www.ipindia.nic.in/iponew/Patent_PharmaProduct_2005_06_2009_10.pdf. If we use 1994 as our cut-off date our main results are unchanged. Specifically, with a 1995 cut-off date 30 percent of the drugs approved between 1995 and 2013 have their earliest priority dates after the cut-off. With a 1994 cut-off the share is 33 percent.

[9] http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012

[10] By definition, drugs approved in 2013 could not appear on this list, so this analysis is based on the subset of drugs approved until 2012.