feature

Patent term restoration for top-selling drugs in the United States

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Patents temporarily protect brand-name drugs from generic competition, but some of the 20-year patent term is used up before marketing approval. To compensate for patent life lost to clinical testing and regulatory review, current law provides patent term restoration (PTR) of up to 5 years. Examining 170 top-selling drugs with a first generic equivalent approved between 2000 and 2012, we found that 49% (83 drugs) received a PTR extension (median extension: 2.75 years) yielding a median total exclusivity period of 13.75 years, compared with 10.0 years for the 87 nonextended drugs. Because PTR substantially prolongs market exclusivity periods, policies that extend non-patent exclusivity periods (which generally run concurrently with patent exclusivity) for less than the extended patent terms of drugs will have little practical impact.

Introduction

Brand-name prescription drugs are usually protected by patents that last 20 years and provide exclusivity in the marketplace. The competition-free period is intended to incentivize private investment in drug development and, during this time, manufacturers charge high prices as they seek to generate profits. The length of the exclusivity period of a drug has important public health implications [1–4], because the expiration of exclusivity allows interchangeable generic drugs to enter the market, generally leading to competition and substantial reductions in price [5–7]. Use of lower-cost drugs improves patient adherence and outcomes [6,8–11].

One key source of debate related to the exclusivity periods of drugs is that the primary patent covering each drug is often obtained shortly after the date of discovery, meaning a substantial fraction of its 20-year duration could have already lapsed by the time the drug has finished clinical trials, FDA review and is approved for widespread use [12,13]. To address manufacturers' concerns that they were unable to enjoy a full patent term, the Hatch–Waxman Act of 1984 created patent term restoration (PTR) [14–19], which allowed brand-name manufacturers to extend the duration of one key patent covering each prescription drug product to compensate for clinical trial and FDA review periods [14–16]. PTR extends the patent term by an amount equal to half the time spent in clinical trials plus the full time of FDA review up to a total of 5 years or a maximum of 14 years after FDA approval, whichever is shorter [20]. Patented drugs undergoing clinical testing at the time the Hatch–Waxman Act was passed were capped at a maximum extension of 2 years, rather than 5 years [3]. Multiple studies have investigated the duration of effective market exclusivity periods of drugs – the number of years between FDA approval and the availability of generic therapeutic equivalents to US patients [1–4] – but it is unknown how frequently PTR applies and what fraction of the market exclusivity periods of drugs are accounted for by PTR extensions. We sought to assess the effect of PTR in a cohort of top-selling drugs.

Top-selling drugs and generic entry dates

A previous study extracted the top 170 medicines (by sales) that experienced generic entry between 2000 and 2012 [1,21]. For each of these drugs, we identified the primary therapeutic area and designation by the FDA as a new drug versus new formulation or use of an existing drug [22]. We labeled the first quarter of generic entry as the one in which a prescription for a therapeutically equivalent generic version of the brand-name drug appeared in Medicaid prescription data aggregated by the Centers for Medicare and Medicaid Services. We relied on Medicaid data to determine generic entry because actual generic entry can occur months or

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years after the generic drug receives FDA approval, for example, because of ongoing patent litigation or settlement agreements made with the affected brand name manufacturer [13,23,24]. We then calculated the effective market exclusivity period of each drug, defined as the difference between the quarter of FDA approval and the quarter of generic entry.

Patent term restoration

We obtained a list of medicine patents that were granted PTR from the US Patent and Trademark Office (USPTO) [25] and cross-referenced it with our sample of top-selling drugs. The USPTO's data included patent numbers, original expiration dates, duration of extensions and PTR-adjusted expiration dates. Additional details about the relevant patents were then retrieved from the USPTO's Patent Full-text and Image Database [26], including the titles, abstracts and claims. From these materials, we judged whether each drug patent appeared to pertain to the active ingredient or to other ('secondary') aspects of the product, such as the formulation or the method of its use for treating specific medical conditions [2,27]. Previous research has shown that patents on the active ingredients of drugs offer stronger protection and that generic companies are often successful when they challenge secondary patents as being invalid [2,21,28].

Pediatric exclusivity

Another statutory provision that extends exclusivity is the pediatric exclusivity program, which provides manufacturers with the ability to earn an additional 6 months of exclusivity when they test their drugs in children in response to a written request from the FDA [17,29]. Unlike other nonpatent exclusivities, which run concurrently with any patent term, pediatric exclusivity is added to the end of the patent term [17]. A record of which patents are associated with these 6-month extensions is available in the FDA's medicine patent register for approved small-molecule drugs (Orange Book), which is published annually [30]. To determine whether the patents receiving PTR were also associated with pediatric exclusivity extensions, we searched using the patent numbers in data files compiled by scholars at Columbia University from previous annual publications of the Orange Book (1980–2012) [31].

Analyses

We tabulated descriptive statistics on the number and proportion of products within our sample that received PTR extensions as well as the duration of those extensions. To further measure the impact of PTR, we compared the number of years of patent life remaining after FDA approval for each drug's key patent with and without PTR extensions. However, this does not account for other factors (non-PTR-extended patents or other manufacturer strategies generally called 'life-cycle management') that can delay generic entry beyond the expiration of the original patents of a drug. Therefore, in a second analysis and to derive an estimate of the effective market exclusivity period without PTR, we subdivided our cohort into two categories: those for which the PTR and pediatric exclusivity extension was 'consequential' for the availability of generic drugs in retrospect (i.e., generic entry coincided with the expiration of the PTR or pediatric exclusivity of drugs); and those for which these exclusivity extensions were not consequential (i.e., generic entry did not coincide with the expiration of the PTR or pediatric exclusivity of drugs). The PTR or pediatric exclusivity extension was deemed consequential if generic entry occurred within the same or subsequent quarter following expiration (i.e., drugs for which the conclusion of the extended patent term was the main determinant for generic entry). By contrast, drugs for which generic entry occurred either much before or much after that quarter (i.e., drugs for which the conclusion of the extended patent term was not the main determinant for generic entry) must have had other patents or market forces driving the timing of generic entry for these drugs. Because those exclusivity periods would not have changed with or without PTR, we deemed those nonconsequential PTRs.

About half of top-selling drugs receive PTR

Among the 170 top-selling medicines in our sample, PTR was granted for 83 (49%). The drugs in this subset were approved between 1986 and 2003 [median: 1995; interquartile range (IQR): 1991–1997]. The drugs represented 15 therapeutic areas with neuropsychiatry having the largest share (22/83, 27%) followed by cardiovascular (14/83, 17%) and infectious disease (13/83, 16%). These disease areas also made up the three largest shares of the non-PTR drug cohort ($n = 87$).

Nearly all patents receiving PTR contained claims related to the active ingredients of drugs (77/83, 93%). The remaining six pertained to methods of treatment (four patents) or manufacturing (two patents). Seventy-eight drugs (94%) were designated by the FDA as having new active ingredients (i.e., new chemical entities), whereas the five others were new formulations of existing active ingredients. Among the 87 drugs without a PTR extension, only 23 (26%) were designated as new active ingredients whereas the other 64 (74%) were designated as new formulations of existing compounds. Of drugs captured in our overall sample with new active ingredient designations, 77% (78/101) received a PTR extension.

Almost three-quarters of drugs with PTR reached their PTR limits

Among the 83 drugs in our sample that earned PTR, the median PTR duration was 2.75 years (IQR: 1.5–4.0). The majority of PTR periods reached the maximums allowed (61/83, 73%). Excluding 17 older drugs that were limited by a transitional 2-year extension limit for drugs that were in development in 1984, 44 drugs remained. Of these 44, 31 (70%) had PTR extension terms that reached the 14-year limit and 13 (30%) reached the 5-year limit. The original patent expiration dates ranged widely with two expiring even before FDA approval (Fig. 1). The addition of the PTR extensions alone shifted the expiration dates of the patents from a median of 9.5 years (IQR: 6.75–11.75) after FDA approval to a median of 13.25 years (IQR: 10.25–14.0) after FDA approval, an increase of 40%. Before the PTR extensions, 20 (24%) patents had 12 or more years of patent life remaining after FDA approval; after PTR it was 51 (61%).

PTR appeared to delay generic entry for about one-quarter of drugs

Among the 83 drugs in our sample that received PTR, generic entry occurred 13.75 years (IQR: 11.0–14.75) after FDA approval (Fig. 2). The median original patent term was 73% of this time, and the median PTR extension represented 21%. In addition to PTR, the majority of these PTR-extended patents (46/83, 55%) was associated with 6-month pediatric exclusivity extensions that represented 4% of the median exclusivity period. Generic entry then occurred a median of 0.25 years (IQR: 0.0–0.75) after the expiration of these extensions, or 2% of the median exclusivity period. The drugs with PTR had a considerably longer median effective exclusivity period as compared with the 10.0 years (IQR: 7.0–14.5) for the 87 drugs in our original sample that did not receive PTR [among those drugs 38 (44%) received the pediatric exclusivity extension].

Generic entry coincided with the expiration of the extended patent for 44 (53%) drugs, or ~26% of the 170 top-selling drugs. For these 44 drugs with presumably highly consequential PTR (and pediatric exclusivity, where relevant) extensions, we found that PTR had effectively extended the exclusivity period by a median of 3.25 years (IQR: 2.0–4.5), moving generic entry from a median of 10.5 years (7.75–12.5) to 14.25

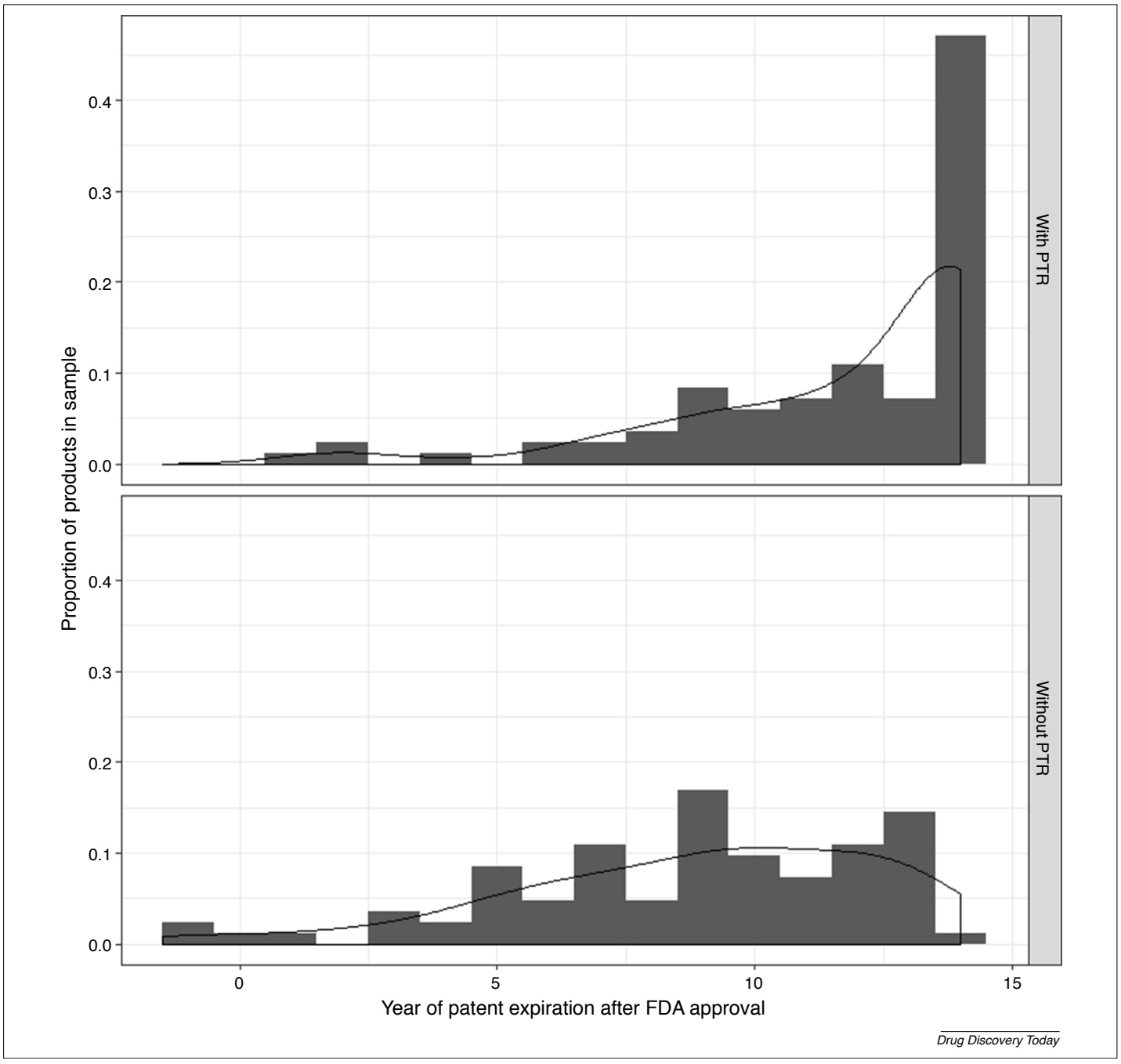

FIGURE 1

Patent term expirations with and without PTR for 83 top-selling drugs 2000–2012. With PTR, adjusted expiration dates were shifted to a median of 13.25 years (IQR: 10.25–14.0). But without PTR, the original expiration dates of the 83 drugs spanned from 2 years before FDA approval (year zero) to nearly 14 years after FDA approval, expiring a median of 9.5 years (IQR: 6.75–11.75) after FDA approval. The most distinctive effect of PTR was to shift a large proportion of the patent term expiration dates to the 14-year limit on patent life after FDA approval.

years (IQR: 12.5–14.75) after FDA approval, an increase of 34%. For the remaining 39 (47%) drugs, PTR did not appear to be as consequential, because generic entry occurred either substantially before (ten, 26%) or substantially after (29, 74%) the expiration of the extended patents. Thus, after adjusting only for the extensions that appeared to be consequential for generic entry (i.e., generic entry coincided with the expiration of the patent extensions), the overall estimated impact of PTR was to shift the effective market exclusivity periods on the 83 eligible drugs from a median of 11.25 years (IQR 8.5–13.5) to 13.75 years (IQR: 11.0–14.75) after FDA approval, a difference of 2.5 years and an increase of 22% (Fig. 3). PTR shifted the number of drugs with effective market exclusivity periods of 14 years or longer from 22% (18/83) to 48% (40/83), and from 43% (36/84) to 70% (58/84) for the number of drugs with 12 years or longer exclusivity.

Policy considerations

PTR extensions have substantially prolonged the effective market exclusivity periods of some top-selling drugs in the past decade, as intended under the Hatch–Waxman Act. Nearly all such extensions were applied to patents covering new active ingredients, as opposed to products with

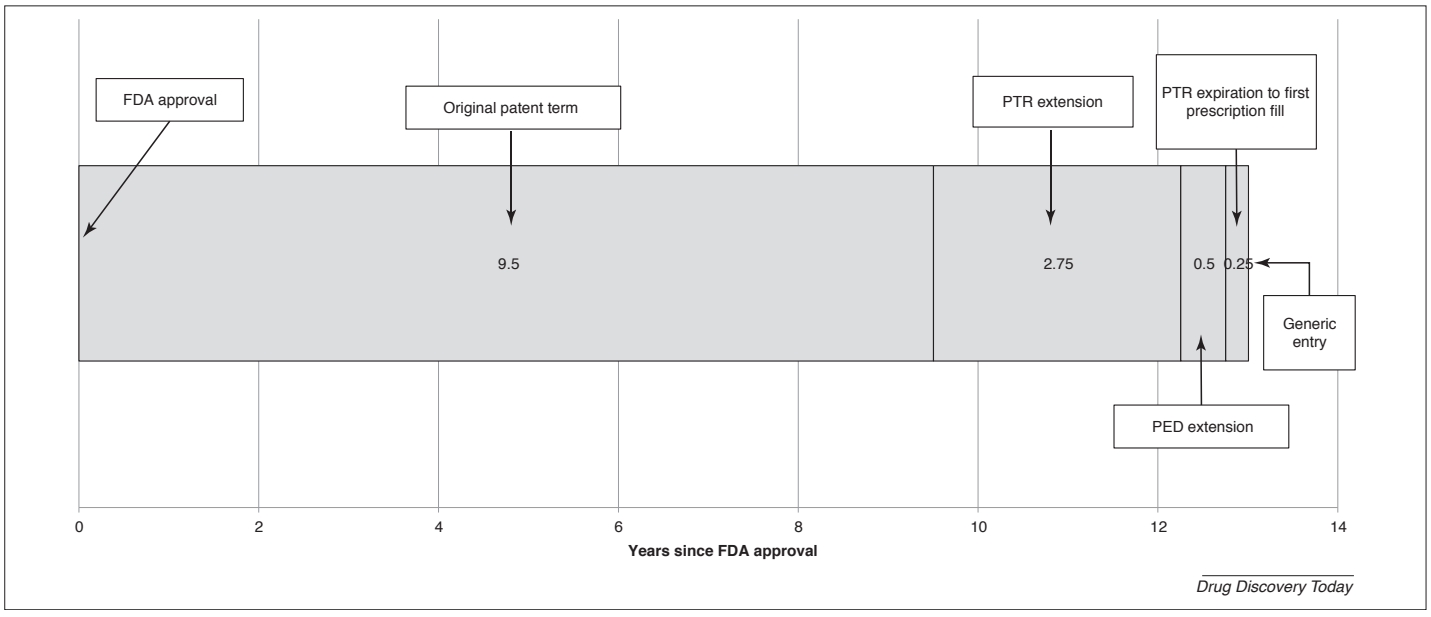

FIGURE 2

Median market exclusivity period segments in a cohort of recent top-selling drugs. Median time segments within the exclusivity period for the 83 products receiving PTR are shown. Since FDA approval, the original patent term of the products expired after a median of 9.5 years. The median product had a PTR period of 2.75 years, which was then further extended by an additional 6-month (0.5 year) pediatric exclusivity. Generic entry (as measured by the first prescription appearing in the Medicaid data aggregated by the Centers for Medicare and Medicaid Services) then occurred a median of 0.25 years later. Although the sum of these medians is 13.0 years, the overall median exclusivity period among the 83 drugs was 13.75 years (IQR: 11.0–14.75) when it is taken directly from the differences between the FDA approval dates and generic entry dates of the drugs.

variant formulations or different uses of existing medicines. Most PTR extensions were capped by the maximum amount of time allowable by law, reaching either the 5- or 14-year statutory limits. For about a quarter of the 170 top-selling drugs in our cohort (or about half of drugs to have received PTRs), PTR and pediatric exclusivity extensions were highly consequential in that the expiration of these extensions marked entry of generic competition. Among these 83 drugs, our most conservative estimate is that PTR prolonged the median market exclusivity period by 22% or a difference of 2.5 years.

Our results align with previous work showing that PTR is most relevant to products containing new active ingredients [14–16]. Therefore, one positive effect of PTR is to magnify the difference in the length of the post-approval exclusivity periods between novel drugs (which generally require more resources for preclinical and clinical testing) and variant formulations or uses of existing drugs (which require fewer such resources). Such a difference helps incentivize investment into new active ingredients that are more likely to represent therapeutic advances.

By extending the exclusivity periods of drugs, PTR also creates substantial costs for patients and the healthcare system. The Medicaid expenditure data used by our study to identify generic entry indicates that, during the consequential market exclusivity extension terms, expenditures totaled US$35.8 billion, an average of US$265.1 million per quarter or US$88.4 million per month. Thus, even very brief extensions can come at a high social cost. We also found that statutory limits on patent extension are highly consequential in that nearly three-quarters of PTR extensions reach the 5- or 14-year maximums permitted by law [18], because, for many of these drugs, time spent in clinical testing and regulatory review was long enough to reach those limits. During the past decade, the trend has been to try to reduce clinical testing periods as much as possible through interventions like the FDA's 'breakthrough therapy' designation, which was created in 2012. In 2016, about three-quarters of new drug approvals were truncated by at least one such accelerated program [32]. Similarly, regulatory review periods have fallen over time from a median of nearly 2 years in 1993 to less than 1 year in 2016 [33]. As overall clinical development and regulatory times fall, drugs may have greater remaining patent terms at the date of approval with fewer PTRs reaching maximum limits. PTR will then become more valuable for drugs that had particularly long development or review times, consistent with the original goals of the Hatch–Waxman Act.

Few generic drugs entered before patent expiration. Irrespective of patent protection, federal law prevents generic small-molecule drugs from being marketed for ~5–7 years after the approval of new drugs [34]. Some policies intended to incentivize development of certain drugs have sought to make this time period longer; for example, in 2012 certain high-value antibiotics were given an additional 5 years of generic-free exclusivity. Our data show that such policies are likely to have minimal impact in either direction owing to the prevalence of PTR and pediatric extensions that protect new drugs for 12 or more years. Other life-cycle management techniques that manufacturers use to extend exclusivity beyond this term include additional patents covering the same drug that were not granted PTR and litigation settlements with generic manufacturers [13].

One limitation of our study is that our observation period still included drugs that had PTR extension terms truncated by the 2-year maximum imposed for drugs that were being tested during the passage of the Hatch–Waxman Act (n = 17). Because this threshold no longer exists, an even larger fraction of newly approved drugs today could be eligible to reach the 14-year limit on patent life after FDA approval than is reflected in our study, assuming the time spent in clinical testing and review has stayed consistent. However, a study with a sample of more-recently approved drugs reported that PTR extensions were expiring a median of 12.3 years after FDA approval and that fewer reached the 14-year limit compared with those in our study [35]. This suggests that, although

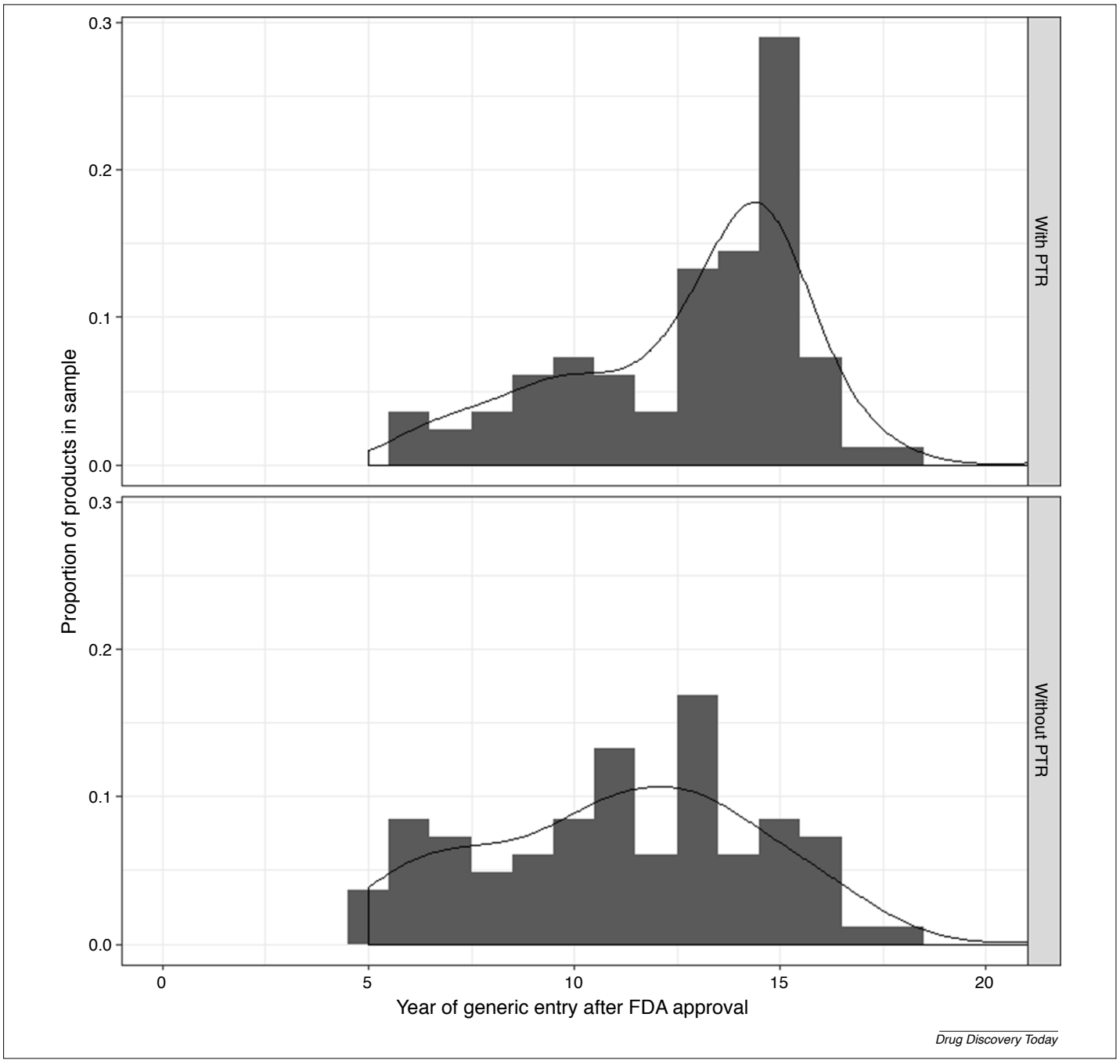

FIGURE 3

Generic entry estimated with and without PTR for 83 top-selling drugs 2000–2012. The year of actual generic entry for the 83 top-selling drugs (shown above) was a median of 13.75 years (IQR: 11.0–14.75). The mark of PTR is readily observable through the large proportion of drugs that experienced generic entry immediately upon the expiration of the extension 14 years after FDA approval (year zero). To estimate when generic entry would have occurred without PTR, we subtracted the PTR extensions, but only in those cases in which generic entry matched the expiration of the extended patent. When generic entry did not match the expiration of the extended patent, we assumed that other patents or market forces were driving the timing of generic entry for these drugs and that the exclusivity periods would not have changed without PTR. We estimate that – without PTR – generic entry would have occurred a median of 11.25 years (IQR 8.5–13.5) after FDA approval. The effect of PTR was to prolong the median market exclusivity period of the 83 drugs by 22% or a difference of 2.5 years.

the 2-year maximum no longer applies, other factors have changed (e.g., shorter clinical testing periods) that enable a 5-year PTR extension without reaching the 14-year maximum on patent life after FDA approval. Thus, whereas clinical testing and review durations have varied over time, PTR has consistently played a major part in prolonging the effective exclusivity periods of new drugs for 12 years or more after FDA approval.

Another limitation of our study is that our sample of drugs includes only top-selling medicines. Timely generic entry upon expiration of the primary patent of a drug is often dependent upon successful challenges to secondary patents that expire at a later date [2,28,36,37]. Primary patents, defined as those covering active ingredients, are most likely to be extended under PTR and are more likely to withstand court challenges as compared with other drug patents. By contrast, so-called secondary patents are often found to be invalid or

not infringed when subject to litigation [2,38,39]. In smaller markets, patent challenges tend to be less vigorous [2,38,39] and later-expiring patents on secondary aspects of medicines more-often extend beyond the expiration of patents with PTR. For these drugs, generic entry might not occur even after all exclusivities expire. Studies on the role of PTRs in smaller markets, therefore, could find that these extensions have less significance.

Concluding remarks

PTR substantially extends the length of the market exclusivity period for top-selling drugs that contain new active ingredients, with the PTR term itself often reaching the current maximum legal limits. Because new formulations or indications are less likely than new active ingredients to receive PTR extensions, PTR extensions magnify the difference in the effective exclusivity periods between these two categories of drugs. Policy proposals aimed at further-extending non-patent exclusivities are unlikely to have much impact on those drugs subject to PTR, because PTR already ensures market exclusivity periods that are typically 12 years or longer and far exceed even the 7-year exclusivity given for newly approved drugs for treating rare diseases [40].

Conflicts of interest

The authors declare that they have no conflicts of interest.

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