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RESEARCH ARTICLE

Polymorphs and Prodrugs and Salts (Oh My!): An Em Analysis of "Secondary" Pharmaceutical Patents

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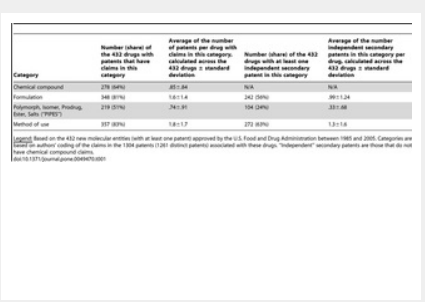
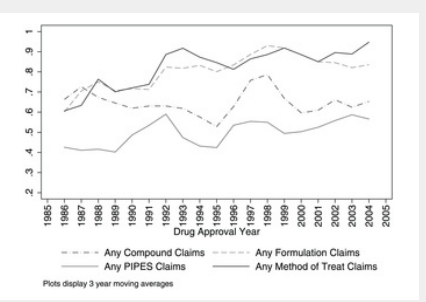
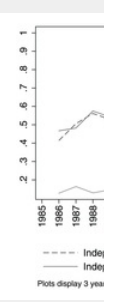
Figures







Abstract

Background

While there has been much discussion by policymakers and stakeh
effects of "secondary patents" on the pharmaceutical industry, the
evidence on their prevalence or determinants. Characterizing the la
secondary patents is important in light of recent court decisions in t
them more difficult to obtain, and for developing countries consider
secondary patents.

Methodology/Principal Findings

We read the claims of the 1304 Orange Book listed patents on all ne
approved in the U.S. between 1988 and 2005, and coded the paten
chemical compound claims (claims covering the active molecule its
several types of secondary claims. We distinguish between patents
claims, and those with only secondary claims and no chemical com
("independent" secondary patents).

We find that secondary claims are common in the pharmaceutical i
that independent secondary patents tend to be filed and issued lat
compound patents, and are also more likely to be filed after the dru
present, independent formulation patents add an average of 6.5 ye
C.I.: 5.9 to 7.3 years), independent method of use patents add 7.4 ye
years), and independent patents on polymorphs, isomers, prodrug,
claims add 6.3 years (95% C.I.: 5.3 to 7.3 years). We also provide evi
independent secondary patents are more common for higher sales

Conclusions/Significance

Policies and court decisions affecting secondary patenting are like
impact on the pharmaceutical industry. Secondary patents provide
patent life in the pharmaceutical industry, at least nominally. Eviden
more common for best-selling drugs is consistent with accounts of
management" or "evergreening" of patent portfolios in the industry

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Introduction

Patents play a distinctively important role in the global pharmaceut
Studies suggest that pharmaceutical firms consider patents critical
recoup R&D investments, much more so than firms in other industri
believed to reflect the difference between the high cost of discover
drugs and the low cost of reverse engineering generic copies of ex
flip side of this is that once drug patents expire, generic competitio
and promote wider access to medicines.

Though the pharmaceutical industry is often cited as the epitome o
industry – one with low patent-product ratios [2] – the number of pa
grown dramatically over the past three decades [6]. Part of this gro
reflects the many types of claims now common in the pharmaceutic
products may be associated, for example, not only with patents cov
compound. They may also be covered by patents covering modifie
compound, medical uses of a known chemical compound, combina
chemical compounds, particular formulations (tablets, topical forms
and processes, among others [6]. This paper examines the rise of t
patents, and assesses their impact on patent life. These patents ar
secondary because they are assumed to come later in the sequen
offer less robust protection than a chemical compound claim. We u
because we believe these patents to be necessarily of lesser impo
because the term is conventional in the literature, and among prac

Secondary patents are interesting for several reasons. First, much
pharmaceutical patents focuses on primary patents, making secon
studied. For example, in several influential studies of effective pate
pharmaceutical sector, Grabowski and Vernon estimate that delays
regulatory review process lead to effective patent terms of approxi
years [9]. Figures such as these are widely reproduced in the litera
patent term extensions and other supplemental forms of market ex
they have a notable shortcoming: they compute patent life based o
available, and generally ignore secondary patents [9]. If secondary
obtained later in the invention cycle than chemical compound pate
underestimate patent life, perhaps substantially. However to our kn

only a few large-sample empirical studies of secondary patents [11

A better understanding of secondary patenting is important, becau perceived by pharmaceutical practitioners as critical to practices o management," and thus to business strategy. As one recent article of any life cycle management strategy ... is to extend patent protec patent term for as long as possible, by filing secondary patents whi keep generics off the market" [7]. Secondary patents also may be b important to industry over time, particularly if declining R&D produc pressure on companies to extract profit from existing drugs. In a re Organization for Economic Cooperation and Development, more tha pharmaceutical companies surveyed reported an increase in pate years before, and many attributed this in part to new efforts to pate they would not have sought to patent ten years before, even if they [13]. A recent European Commission report offers a compatible acc pharmaceutical executive, who characterized the situation prior to as one where products were "mainly [chemical entities] which wher patent," and the period of the late 1980s to early 1990s as one cha "[e]xpansion of the portfolio to cover lifecycle initiatives, to extend p product and the brea[d]th of the protection trying to keep competiti

The flip side of this is the widespread allegation that secondary pat "evergreening" strategies to extend monopoly protection on existi term evergreening is used to refer to a range of practices. Some ar patent strategy [14]–[16], but others depend importantly on second example, such patents may be listed on the FDA's Orange Book and opportunities for automatic injunctions against generic competitors

Secondary patents are also interesting because some have argue secondary claims lack true inventiveness and should not be grante medical uses have at various points been controversial in Europe, l European Patent Convention's exclusion of patents on methods of Many developing countries outright forbid patents on new uses of l [10]. Patents on enantiomers of known racemic chemical compoun forms" of known substances, have been viewed as obvious or non- Concern about non-innovative secondary patents in pharmaceutic one, across industries, that resource constrained patent offices ma number of low quality patents, i.e. patents that would not have beer to proper scrutiny [18].

Not surprisingly, policymakers are also interested in the implication patents. For example, a recent European Commission inquiry consi secondary patents in the pharmaceutical sector, and concluded th companies appear to use them specifically to inhibit generic compe that they are perceived as generally weak patents [6]. Similar ques by the U.S. FTC [19]. Recent court decisions may make secondary p obtain in the U.S., with unknown implications for the industry [8], [20 are also at the center of current controversy in India, where the new patents on new uses, combinations, and new forms of known subst

increase efficacy [21]. India's example has recently been followed l
developing countries [21].

How big of a difference would policies restricting secondary patent
landscape in pharmaceuticals? What precisely might be at stake if
strengthened in a way that casts doubt over certain classes of sec
answer to these questions, and the other policy questions discusse
information on the prominence and impact of secondary patenting
currently lacking. This paper aims to begin to fill this void. We provi
to address the following questions: What is the prevalence of pater
compound claims, patents with secondary claims, and of "independ
patents that have no chemical compound claims? When are chemi
independent secondary patents filed, relative to drug approval? W
these patents on the patent life? And does the prevalence of indep
patenting vary with sales?

Data and Methods

Drug data

We began by collecting data on the 528 new molecular entities (NM
U.S. Food and Drug Administration between 1988 and 2005, from th
database. According to FDA definitions, NMEs are drugs where the
not previously approved by the agency [22].

Sales

To examine how propensity to obtain secondary patents varies wit
generated national estimates of sales for the drugs in our sample b
from the Prescribed Medicines File of the Medical Expenditure Pane
obtained these data annually for the 1996–2010 period.

We are interested in the effects of sales on propensity to obtain dif
One difficulty is that patents may also affect drug sales, for exampl
generic entry. Accordingly, we use sales estimates from a point in t
when generic entry is not possible: in the fifth year after a drug is a
time, generic competition is typically not possible even absent pate
to "data exclusivity" restrictions on generic entry. (Data exclusivity i
marketing rights that stem not from the patent system, but from the
system. Some countries, such as the U.S., award periods of data ex
submission of certain clinical trial data.) Previous analysis [24] of fir
on NMEs over the 2001–2010 period shows no instances of generic
year after NME approval.

Since our sales data are for 1996–2010, collection of sales in year
analyses of sales, we limit the sample to the 342 NMEs (that have at
were approved between 1991 and 2005. We adjusted sales to 201

using the commodities PPI (Producer Price Index) deflator.

In the analyses of sales, we group drugs by sales quartiles. This allo
relationship between sales and patenting with a flexible functional
important in this industry since high-selling "blockbuster" drugs are
different patent dynamics than others [24]. It also reflects the pract
sales figures are estimates based on a sample, and we cannot dete
with no reported sales in MEPS actually have zero sales, or instead
MEPS lacks the statistical power to detect. The bottom sales quartile
no sales" drugs.

Orange book patent data

We combine the drug approval data with patent data from another
Orange Book, a compendium of patents pertinent to approved drug
information provided to the agency by the originator firms [25]. We
patents on drugs from the machine-readable versions of the FDA's
Electronic Orange Book") released between 2000 and 2009. Since
Orange Book list only unexpired patents, we also obtained a file wit
expired patents (from pre-2000 versions) from the FDA, via a Freedo
request. (We verified the FOIA data on older expired patents agains
previous Orange Books published from 1988–2000, and found the
substantially in agreement, with the exception of what appear to be
the printed versions.) For each drug, we thus collected information
unexpired patents that were listed in the Orange Book.

Overall, the 528 NMEs map to 1261 distinct patents, and 1304 total
a patent can be associated with multiple NMEs. For example, the pro
is listed on the Orange Book for two drugs Omnipaque (iohexol) 180
and Visipaque (iodixanol) 270, approved in 1996.) And some NMEs
on the Orange Book: drugs without patents tend to rely on other for
for market protection, e.g. Orphan Drug exclusivity.) Since our focus
exclude these drugs from our analysis.

Expiration dates

From the Orange Book, we determined the expiration dates for each
Orange Book listings reflect the statutory term, as well as patent ex
term adjustments. Since expiration dates for patents sometimes ch
grant of special exclusivity periods such as those offered in compe
trials) we take the maximum expiration date for each drug-patent o

Application and issue dates

We obtained information about the application date and issue date
patents from the United States Patent and Trademark Office's *Cassi*
patents [26].

Patent coding

We read through each claim in these patents, and determined whe
one or more of the following types of claims:

- *Chemical compound* claims: those claiming an active ingredie
previously been disclosed in the art.
- *Formulation* claims: those directly onclaiming specific pharma
to administer a product (e.g. tablets, dosage forms, sustained
- *Method of treatment/use* claims: methods of treating specific d
with particular compounds
- *Polymorph, Isomer, Prodrug, Ester, Salts ("PIPES")* claims: mino
structure or chemical makeup of a molecule

To do so, two of the authors [CP and AK] initially each independently
hundred of the same patents to clarify the categories and then divi
each patent coded by one person). As a check on accuracy, patent
(typically, those claiming either a compound or a new form of a kno
re-coded by research assistants with doctoral degrees in chemistry
pharmaceutical patenting.

The Appendix S1 discusses the categories and coding rules in deta

Chemical compound claims represent primary claims, and the other
secondary claims. An individual patent can (and often does) have c
one of these categories. For example, the first filed patent on a drug
chemical compound claims as well as one or more types of second
distinguish between such patents and those with purely secondary
determined which patents were "independent" secondary patents,
claims only. We make this distinction since patents with independen
are those that are most important for discussions of evergreening,
claims in patents that also have chemical compound patents do no
patent life.

Under this definition an "independent formulation patent" can also
secondary claims, e.g. PIPES claims. Note also that we use the term
differentiate these claims/patents from primary (chemical compoun
characterization as "secondary" is not meant to imply anything abo
relationship to chemical compound patents, though we will show th
secondary patents are generally obtained later in the product life c

For drugs with an independent secondary patent we calculated inc
generated by each such patent. In cases where a drug has a chem
and an independent secondary patent of a particular category, the
associated with that category is defined as the difference between
last expiring patent in that secondary category and the last expiring
patent. Where there is no chemical compound patent, incremental
difference between the expiration of the last expiring patent in that

and the expiration of the regulatory exclusivity period for the drug (
five years after the drug is approved) after which generic entry can
behind these measures is to examine the incremental life generate
secondary patents, as compared to that sustained by other forms o
compound patents or regulatory exclusivity).

As we note in the Table S1, other types of claims–process claims, pr
claims, medical device claims, particle sizes, combinations, and pur
but excluded from analyses, since they are individually small in nur
these categories are reasonably considered secondary claims, our
provide conservative estimates of the prevalence of secondary pat
discussion we offer additional reasons that our method is likely to u
overstate, the importance of secondary patents.

Analytical methods

Using these sources and measures, we determined (1) the share o
compound patents and different types of secondary claims; (2) the
each type of independent secondary patent; (3) the share of drugs
compound patents and different types of secondary claims, by app
share of drugs with each type of independent secondary patent, by
timing of filing/issue of chemical compound patents and each type
secondary patent; (6) average incremental patent life generated by
independent secondary patent; and (7) the share of drugs that hav
patents and independent secondary patents, by sales quartile. In a
descriptive data, we estimate logit regressions relating independen
to sales, controlling for application year effects.

Descriptive Results

The prevalence of secondary patenting

The first column of results in Table 1 shows the share of drugs with
claims in a given category. Less than two-thirds of the drugs have c
claims in one or more of their patents. This reflects that the active s
be "new" to the FDA (never before approved for use in humans) yet
arts. Formulation and method of treatment/use claims are quite pre
of drugs with such claims is higher than the share with chemical co
claims are less common, but still present in about half of all drugs. T
shows similar trends in the average number of patents per drug, by

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Table 1. Chemical compound and secondary patents for drugs in

https://doi.org/10.1371/journal.pone.0049470.t001

The third results column focuses on independent secondary paten secondary claims and no chemical compound claims. The majority independent secondary formulation or method of treatment/use pa quarter have standalone PIPES patents. (Recall there is double-cou three categories, so a patent with both formulation and PIPES claim The final column shows similar trends in the average number of ind patents per drug, by category.

Figure 1 shows that the share of drugs with chemical compound cla their patents, by drug approval year, is fairly constant over time. Th chemical compound claims is about 65 percent in both the first thre (1985–1987) and the last three years (2003–2005). Across these sa with formulation claims increased from 60 percent to 84 percent, th claims increased from 43 percent to 57 percent, and the share with claims increased from 61 percent to 95 percent.

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Figure 1. Share of drugs with chemical compound and secondary approval year (three year moving averages).

Based on the 432 new molecular entities (with at least one pater U.S. Food and Drug Administration between 1985 and 2005. Cate on authors' coding of the claims from the 1304 patents (1261 dis associated with these drugs. “PIPES” refers to Polymorph, Isome and Salt claims. The horizontal axis is drug approval year. The v measures the moving average of the share of drugs in an appro least one patent in a category.

https://doi.org/10.1371/journal.pone.0049470.g001

Figure 2 focuses on independent secondary patents. It illustrates th with independent formulation patents has increased over time, as h independent PIPES patents and independent method of treatment/ Comparing the same cohorts as above, the share of drugs with inde patents increased from 41 percent to 55 percent, the share with ind patents from 13 to 23 percent, and the share with independent met

claims from 47 to 80 percent.

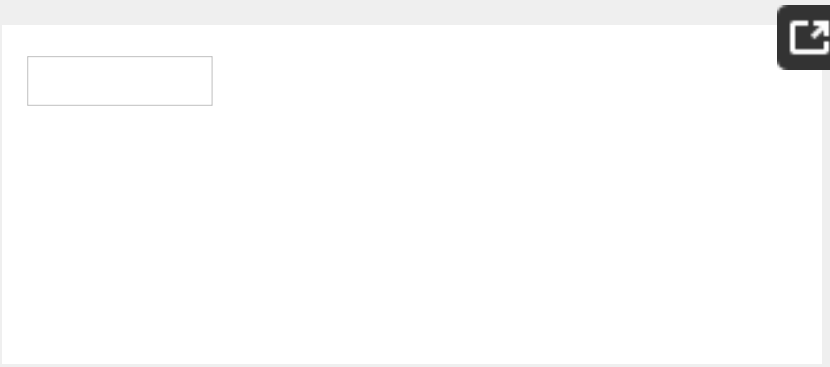

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Figure 2. Share of drugs, by approval year, with independent sec
Based on the 432 new molecular entities (with at least one pater U.S. Food and Drug Administration between 1985 and 2005. Cat on authors' coding of the claims from the 1304 patents (1261 dis associated with these drugs. "PIPES" refers to Polymorph, Isome and Salt claims. "Independent" secondary patents are those wit compound claims. The horizontal axis is drug approval year. The measures the moving average of the share of drugs in an appro least one patent in a category.
https://doi.org/10.1371/journal.pone.0049470.g002

Timing of independent secondary patents

Above we have used the term independent secondary patents to re formulation, PIPES, and/or method of treatment claims but not chem We also looked at when the patents were filed (and issued) relative approval, to see if they are, in fact "secondary" in the sense of later the share of chemical compound patents and independent second category that are filed or issued after the drug is approved. Consist expectations, the vast majority of chemical compound patents are f FDA approval. By contrast, a higher share of independent secondar approval, and about 46 percent (overall, across all types of second approval.

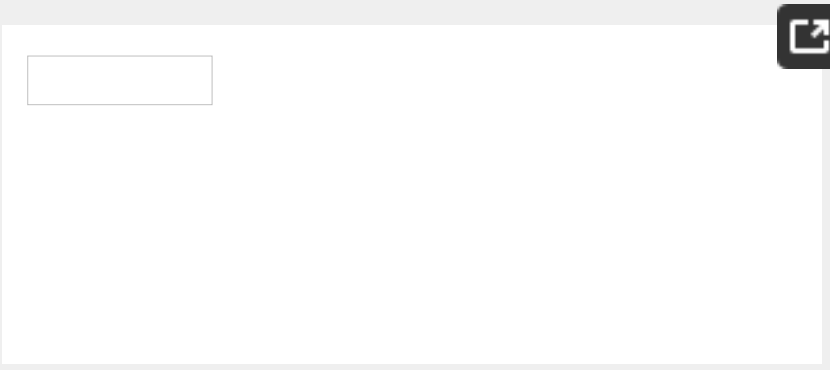

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Table 2. Timing of patent filing and issue relative to drug approv
https://doi.org/10.1371/journal.pone.0049470.t002

Effects of secondary patents on patent term

That independent secondary patents tend to be filed and issued la possibility that they may be important in extending the total exclusiv since patent term in the U.S. runs from the longer of 20 years from a from issue for pre-1995 patents, and 20 years from application for p

Table 3 shows that each of these types of independent secondary with additional nominal patent term. The first column of results show where they are present, generate between four and five years of a beyond chemical compound patents, on average. For the drugs wit compound patents but with independent secondary patents (about the sample), the incremental life is larger, not surprisingly. Across a without chemical compound patents, the average increment range PIPES patents) to 7.4 years (for use patents).

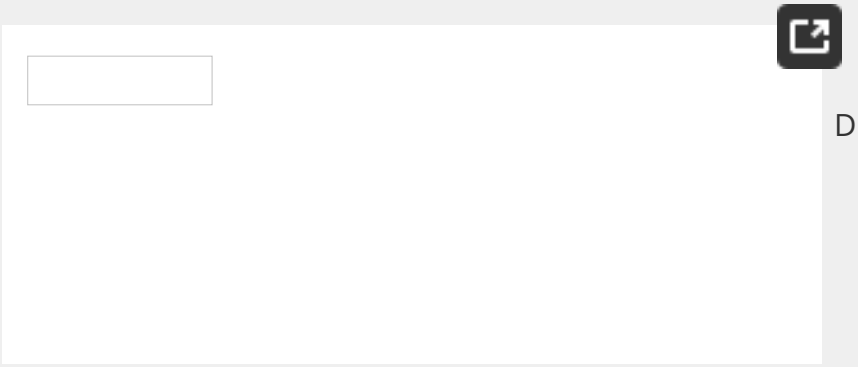

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Table 3. Average incremental patent life from independent secon type.

https://doi.org/10.1371/journal.pone.0049470.t003

Sales

Finally, we examined how the propensity to obtain chemical compo independent secondary patents varies by the branded drug's sales interested in how sales affect the propensity to obtain these patent independent secondary patents filed after the branded drug was a market expectations are more certain.

Figure 3 shows the share of drugs that have one or more (post-app given category. Overall, and consistent with the patent level analys figure shows that few drugs have patents with chemical compound after drug approval, and there is only a slight increase over the sale none in the first quartile to 3.5 percent in the top quartile. There is a firms' propensity to obtain independent secondary patents for high share of drugs with independent (post-approval) formulation paten percent to 26 percent between the bottom and top sales quartiles. drugs with independent PIPES patents (3 percent versus 15 percen method of treatment/use claims (13 percent versus 32 percent) incr bottom and top sales categories.

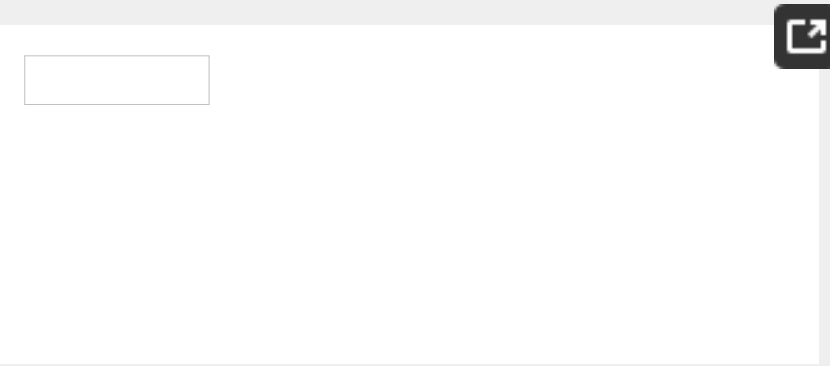

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Figure 3. Share of drugs, by sales quartile, with chemical compo independent secondary patents that are filed after drug approva Based on the 342 new molecular entities (with at least one pater U.S. Food and Drug Administration between 1991 and 2005. Cat on authors' coding. "PIPES" refers to Polymorph, Isomer, Prodrug claims. Independent patents are those with no chemical compou categories are based on national estimates of sales (using infor Medical Expenditure Panel Survey) in the fifth year after brand d horizontal axis is quartile of sales. The vertical axis is the share with at least one patent in a category.

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Regression analyses

In addition to the descriptive analyses, we examine the effects of sa independent secondary patenting through logit regression models whether a drug has any post-approval claims of a given type to sale approval year. Table 4 shows the results. In each of the models dru category are significantly more likely to have such patents than the bottom sales quartile), and the point estimates are largest for the to that post-approval secondary patenting is most common for the hig While logit coefficients are difficult to interpret directly, marginal eff Model 4) show that drugs in the top sales category have an 18 perc likelihood of having any post-approval independent secondary pat category.

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Table 4. Logit models relating whether a drug has post-approva secondary patent claims to sales and approval year.

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The coefficient on the approval year variable is negative and not st
suggesting no significant time trend. This may reflect that the incre
post-approval secondary patenting occurs before 1991 (the first ye
sales data); it could also reflect that these patents are particularly s
censoring since they are filed relatively late in a drug's lifecycle. Su
available on request, show that these results, and the estimated ef
robust to including indicators for each approval year instead of a lin

Discussion

Although secondary patents are often criticized, they are rarely stu
analysis of the role and effect of secondary patents in the pharmac
effort to help inform the important policy debates that surround the
attempt here to mediate between those who favor and oppose sec
different types, but instead offer an empirical picture of what is at s

We show, first, that patents with secondary claims are extremely co
common than chemical compound patents, for the new molecular e
While it is sometimes assumed that a new active ingredient is assoc
compound patent, for example, we show that if an NME is associate
the vast majority are), it is more frequently associated with a formul
drugs) or a method of treatment/use patent (83%) than with a chem
(64%). Patent claims covering new forms of known substances (PIP
common, present in half of all drugs (51%).

Moreover, independent secondary patents tend to come later than
measure both forms of patents against the baseline of drug approv
effectively all chemical compound patents are filed before drug ap
enough that only 11% issue after the approval date. By contrast, se
to be filed later, with nearly one in five secondary patents filed afte
by the FDA, and close to half issuing after the approval date.

Independent secondary patents on average add substantial time to
terms enjoyed by drugs. For drugs that have chemical compound p
patents add on average between 4 and 5 years of additional nomin
that do not have chemical compound patents rely much more subs
patents for exclusivity: here, when there are secondary patents, the
average of 9 and 11 years of patent term beyond the standard data

Moreover, our analysis of patents filed after drug approval reveals
secondary patents are not randomly distributed. Firms' propensity t
secondary patents after drug approval increases over the sales dis
they reflect deliberate attempts by branded firms to lengthen their
lucrative drugs.

Our results are particularly notable because our sample and data a
minimize the importance of secondary patents. Most importantly, ou

includes NMEs. While we have not analyzed this here, we believe n
extensions) are less likely to have chemical compound patents, an
on secondary patents. Second, as noted above we observe a rise i
over time despite censoring. Third, our data excludes certain kinds
in particular, process patents are not listed on the Orange Book. In
suggest that process patents may play an important role in life-cycl
strategies [7]. A recent analysis of secondary patents on two antire
large number of unlisted patents, including but not limited to proce

One factor that our analysis does not incorporate is litigation. Seco
more vulnerable to attack than chemical compound patents, and if
invalidated or designed around, they will in practice have less effe
than their effects on nominal patent life suggest [11], [24]. There is
this is the case. Although industry groups reject the suggestion tha
are weaker than chemical compound patents, in practice companie
patents often appear to hold this view [6]. Previous empirical work
non-active ingredient patents, particularly those that generate incr
much more likely to attract patent challenges in the U.S. [11], [24]. A
study of the sector recently concluded that generic litigation "mainl
patents," and that generic companies have high success rates in c
secondary patents [6].

Even if secondary patents are perceived (and perceived correctly)
than chemical compound patents, this does not mean that they are
effects. A patent that is ultimately invalidated could still yield substa
originator company. Patent litigation in the pharmaceutical industry
and resource intensive, and becomes more so where more patents
involved. This reduces the potential pool of competitors to those wi
wage multi-year patent battles. Such litigation may take several yea
European Commission [6] estimates almost three years for an aver
U.S. a secondary patent may provide the basis for an automatic 30-
approval under the Hatch-Waxman Act. This again comports with a
the industry, such as this one expressed by a pharmaceutical exec
originator company: "Secondary patents will not stop generic comp
may delay generics for a number of years, at best protecting the or
a period of time" [6]. It is possible that even a weak secondary pate
after litigation could produce years of valuable exclusivity, though t
empirical question.

Furthermore, litigation as a means to invalidate weak secondary pa
plausible policy outcome in countries without robust incentives for
the expense of challenging these patents. Insofar as the policy res
secondary patents relies on litigation and rigorous patent examina
ensure that only truly inventive secondary patents issue, resource-
likely to be at a substantial disadvantage [21].. This may help to exp
India have sought to adopt clear statutory bars on certain types of
claims, even if those bars are not always consistently implemented
examination [28].

Our data also reveal the stakes of the decision that developing cou
about the permissible scope of patents. Although the World Trade O
Related Aspects of Intellectual Property Agreement does require m
adopt patent protection for medicines, its requirements are genera
require countries to permit secondary patents [21]. We can quantify
decisions: If the future looks like the past (and the patent landscape
that in the U.S.) a conservative estimate is that eliminating seconda
up 36% of new medicines for generic production, since only 64% of
had patents with chemical compound claims. Additionally, for those
under patent because a chemical compound claim exists, exclusion
patents could limit the duration of patent protection by 4–5 years. T
study reveals the very substantial implications of new trade agreem
now underway for a new "Trans-Pacific Partnership" treaty, and the
proposed barring exactly the kind of limits on secondary patents ad
under consideration by other countries.

Finally, our data also have relevance to the evolution of patent law i
countries. Recent court decisions in the U.S. have seemed to signal
approach to at least certain secondary patents in the U.S. [29]. Whil
address whether such a change would on balance do more to harm
undermining innovation) than to help (by improving access), we do
substantial stakes of this debate.

While the data provided here can be interpreted in different ways, i
advance the policy debate in several ways. Most importantly, it sho
secondary patents are of substantial importance in the industry, an
focus only on chemical compound patents will tend to substantially
breadth and range (term) of patent coverage in the pharmaceutica

Supporting Information

Table S1.

Description of patent claim categories.
https://doi.org/10.1371/journal.pone.0049470.s001
(DOCX)

Appendix S1.

Description of patent claim categories.
https://doi.org/10.1371/journal.pone.0049470.s002
(DOCX)

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Author Contributions

Analyzed the data: BS AK CP. Wrote the paper: BS AK CP. Coding of p

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