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Secondary Patenting Of Branded Pharmaceuticals: A Case Study Of How Patents On Two HIV Drugs Could Be Extended For Decades

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ABSTRACT Pharmaceutical manufacturers rely on patents to protect their intellectual property and often seek to extend market exclusivity for their products to maximize their return on investment. One method is by obtaining patents on features other than the original active drug ingredient, including secondary patents on alternate formulations of the drug or on methods of administration. This article examines how secondary patents can extend market exclusivity and thus delay generic competition, using as an example two key antiretroviral drugs for the management of HIV: ritonavir (Norvir) and lopinavir/ritonavir (Kaletra). We identified 108 patents, which together could delay generic competition until at least 2028—twelve years after the expiration of the patents on the drugs' base compounds and thirty-nine years after the first patents on ritonavir were filed. Some of the secondary patents that were reviewed were found to be of questionable inventiveness. We argue that increased transparency for existing patents, stricter patentability standards, and increased opportunities to challenge patent applications and patents could reduce inappropriate market exclusivity extensions on brand-name drugs and open the door to lower-cost generics.

The process of developing new prescription drugs has long been intertwined with the US patent system. To earn a patent, an invention must be novel and constitute what patent law refers to as a “nonobvious” advance over current knowledge in the field. Pharmaceutical manufacturers rely on patents to protect their intellectual property: Patents provide market exclusivity during the patent term, which is twenty years from the patent application date. During this competition-free period, manufacturers charge higher prices for their products to recoup their initial investment in development and testing.¹ After this period, less expensive generic versions can come on the market and become widely available.²

Pharmaceutical manufacturers therefore have

an incentive to extend market exclusivity for their products as long as possible.³ One common strategy is to obtain additional patents beyond the original patents that protect the drug's underlying active ingredient and disease targets. These “secondary” or “later-issued” patents may protect peripheral features of the product (such as a tablet's coating),⁴ metabolites or alternative crystalline forms of the product,⁵ or methods of use (such as a method of treating disease).⁶ In the pharmaceutical sector, this practice is called “life-cycle management;” it is also sometimes referred to as “evergreening.”⁷

A key question is to what extent these later-issued patents protect valid features or methods, instead of serving as a business strategy to delay generic competition. In some cases, the patent claim may be weak or largely duplicative of an

already patented feature or product. These patents can increase what it costs for a manufacturer to bring a generic version of a drug to market and effectively delay approval of the generic drug after the patents on the underlying base compound expire.

As an example, the US patent on the active ingredient in the proton-pump inhibitor omeprazole (Prilosec) expired in April 2001, but the manufacturer received later-issued patents on the pill's coating that lasted until 2007 and beyond. Manufacturers seeking to market competing generic versions had to challenge these patents in court. The litigation process helped further delay the release of competing versions.⁴

Extending market exclusivity in this way can have important public health implications. Studies show that high prices for brand-name drugs can reduce access to certain essential drugs, affect patients' adherence to treatment regimens, and raise overall health care spending.^{8,9} Pharmaceutical spending has stretched the budgets of government-funded insurance programs such as Medicaid,¹⁰ and some programs have limited the coverage they provide and have increased patient copayments or deductibles, which reduces the use of clinically necessary drugs.^{11,12}

Although secondary patenting is both common and controversial, few researchers have rigorously analyzed this practice. Much of the literature on the topic broadly describes life-cycle management strategies, such as the use of patents on drug enantiomers (mirror-image forms of drug structures)¹³ or the outcomes of specific lawsuits in which a generic manufacturer sought to overturn a secondary patent.¹⁴ A more in-depth understanding can shed light on how long later-issued patents can extend the period of market exclusivity, and on the characteristics of such patents.

In this study we focused on the protease inhibitors ritonavir (Norvir) and lopinavir/ritonavir (Kaletra). These inhibitors are widely used with patients infected with HIV-1 and have become part of first- and second-line therapy regimens for such patients worldwide. Our goal was to systematically identify and classify all US patents covering these products. We also gauged some of the patents' quality and considered whether there were cases of overlapping patenting, in which separate patent applications or granted patents may not be considered inventive.

Study Data And Methods

PATENT SEARCHING Patent applications and issued patents from many countries are now available in searchable online databases, which

means that a systematic approach to describing the role of patents in life-cycle management is now possible. We first identified US patents and patent applications protecting ritonavir, lopinavir, and lopinavir/ritonavir—the combination of the two protease inhibitors. We chose to focus on US patents because the United States is a lucrative market for pharmaceutical products. Therefore, we would expect manufacturers to maximize their pursuit of US patents.

Abbott Laboratories' Norvir (ritonavir) was approved by the Food and Drug Administration in 1996, and its Kaletra (lopinavir/ritonavir) was approved in 2000. Lopinavir has never been approved as a single entity in the United States.

As a data source, we used the Thomson Innovation database of US patent applications and granted patents. We included patent applications because nearly all patent applications in the pharmaceutical sciences are ultimately granted¹⁵ and the period of market exclusivity starts from the date of application.

To ensure the broadest possible results, we conducted ten separate searches of the Thomson database using key terms commonly associated with ritonavir, lopinavir, and lopinavir/ritonavir. We also searched for all Abbott-affiliated inventors listed on a relevant patent. Because this case study focused on a single manufacturer's patent strategy, we obtained only patents assigned to Abbott, rather than to its subsidiaries. Patent searches were conducted up to April 2011, with final checks of the status of identified patents completed in December 2011. More details of the patent search process are included in the online Appendix.¹⁶

PATENT SELECTION We included any patent or application that claimed any pharmaceutical component of ritonavir, lopinavir, or lopinavir/ritonavir, or any product related to these compounds. We cross-checked the search results to ensure that they included the patents listed by Abbott in the *Orange Book*, a listing of drugs approved by the Food and Drug Administration, equivalent generic drugs, and patents protecting them.¹⁷

Further checking for applicable patents was conducted by querying the International Patent Documentation Center (INPADOC, an international patent collection containing patent families and legal status information) patent families through the espacenet database,¹⁸ a free online service for searching patents and patent applications. We also examined all citations for each of the identified patents using Thomson Innovation and espacenet. These searches identified no additional relevant patents for inclusion in our final sample.

PATENT LANDSCAPE ANALYSIS After removing

duplicates, we analyzed the remaining patents and applications. First, we noted the application and expiration dates of each patent, including any patent term adjustments and extensions for granted patents. Patent term adjustments and extensions compensate manufacturers when the exclusivity period for certain patents is truncated because of delays in the consideration of a patent application, or when it takes the Food and Drug Administration longer than anticipated to review and approve the product application.

For active patents that had not yet expired, we used the Patent Application Information Retrieval of the US Patent and Trademark Office¹⁹ to identify whether they had been reversed, abandoned, or abandoned and then refiled as a continuation application. Applications that were abandoned and then refiled were counted only once.

With the help of a pharmaceutical scientist, we categorized the subject matter claimed by each patent using descriptive analysis.²⁰⁻²² First, we developed a structured instrument for classifying patents into major descriptive categories and subcategories. Next we conducted an independent preliminary review of the patents and refined the instrument.

Then we assigned each patent to one or more of the following four categories that could be applied to ritonavir or lopinavir: related chemical structures and compositions or formulations; manufacturing methods and processes; methods of treatment of HIV infection and other diseases; and general patents. Some patents fit into multiple categories, such as a patent claiming both a formulation for lopinavir/ritonavir and a process for making the formulation.

Finally, we reviewed the claims of each patent in each category and determined their similarity to the claims of other patents in that category. We also compared the claims to general knowledge available in the field at the time, based on the published literature. Our goal was to determine whether some patents seemed duplicative or lacking in the level of innovation that is technically required of patentable discoveries.

LIMITATIONS As is the case with all patent searching methodologies, ours has a number of limitations. Despite our efforts to conduct a comprehensive search, we may have missed some patents or applications. For example, because patent applications in the United States are usually published eighteen months after the earliest filing date, patent applications filed less than eighteen months before the search date were not captured. Also, patent applications that were withdrawn before publication will not be picked up in any search.

Finally, our search was limited to patents di-

rectly held by Abbott Laboratories. Hypothetically, if subsidiaries or companies controlled by Abbott were the named assignee on patents covering versions or uses of the drugs, these would not have appeared in our searches but could contribute to the market exclusivity period.

Study Results

We identified 108 total granted patents and patent applications. Of these, eighty-two (76 percent) were granted patents, and twenty-six (24 percent) were applications. Four of the granted patents (5 percent) had already expired. Five of the applications (19 percent) were subsequently abandoned, and another six (23 percent) had been abandoned and then refiled.

The base compound for ritonavir was covered by patent number 5,541,206 (filed in 1995), originating from patent applications dating back to 1989. Including patent term adjustments and extensions, the expected patent expiration for the active ingredient in ritonavir is 2014. The patent for the active ingredient in lopinavir was first filed in 1995 (patent number 5,914,332) and has an expected expiration date of 2016.

Because the four broad categories for the 108 patents and patent applications are not mutually exclusive, some of the patents and applications in Exhibit 1 are listed in more than one category ($N = 210$).

RELATED CHEMICAL STRUCTURES AND COMPOSITIONS OR FORMULATIONS The largest category of patents and applications—81 out of 210, or 39 percent—covered chemical structures and drug compositions or formulations related to the base compounds of the drugs (Exhibit 1). We divided these patents into the following four subcategories: compositions or formulations of the drugs individually or combined with other compounds; intermediate compounds useful for the preparation and synthesis of the base compounds; polymorphs; and prodrugs. The last two subcategories are explained below.

Within this broad category, forty-nine of eighty-one patents (60 percent) addressed variations in the composition or formulation of the base compounds. For example, ritonavir and lopinavir/ritonavir were originally sold in the United States as a soft-gelatin capsule formulation. This formulation was abandoned in the case of lopinavir/ritonavir in 2005 and replaced with a tablet form that is heat stable—in other words, it does not require refrigeration. Twenty-two patents (27 percent) in the category covered intermediate compounds.

Four patents (5 percent) covered polymorphs, which are alternate crystalline forms or amorphous solid forms of a base compound. Poly-

EXHIBIT 1
Patents And Applications Covering Ritonavir And Lopinavir/Ritonavir

Patent categories	Ritonavir	Lopinavir	Lopinavir/ritonavir	Ritonavir and/or lopinavir with other compounds	Total
Total	— ^a	— ^a	— ^a	— ^a	210
Base compound or active ingredient	1	1	0	0	2
RELATED CHEMICAL STRUCTURES AND COMPOSITIONS OR FORMULATIONS (81)					
Composition and formulation ^b	18	9	15	7	49
Intermediate compounds	13	9	0	0	22
Polymorphs	2	2	0	0	4
Prodrugs	2	2	1	1	6
MANUFACTURING METHODS AND PROCESSES (68)					
Processes ^c	36	27	5	0	68
METHODS OF TREATMENT OF HIV INFECTION AND OTHER DISEASES (31)					
First method of treatment or administration for HIV	4	4	5	5	18
New uses for HIV or other diseases	6	1	1	5	13
GENERAL PATENTS (28)					
General formulations	— ^d	— ^d	— ^d	— ^d	5
Processes and methods for preparing general formulations	— ^d	— ^d	— ^d	— ^d	11
Other technologies or test systems	— ^d	— ^d	— ^d	— ^d	12

SOURCE Authors' analysis. **NOTE** Intermediate compounds, polymorphs, and prodrugs are defined in the text. ^aNot applicable. Because the categories are not mutually exclusive, patents with claims in more than one category are listed more than once. ^bIncludes combinations with other HIV-treating compounds, salt forms, ester derivatives, and dosage forms. ^cProcesses for making analogs, intermediates, formulations or compositions, and polymorphs. ^dGeneral patents that could be applied to ritonavir, lopinavir, or both.

morphs may affect the drug's physical properties and pharmacokinetic characteristics, such as its stability, solubility, dissolution rate, absorption, and bioavailability.

Six patents (7 percent) were related to prodrugs, which are inactive compounds that become active drugs once they are metabolized.

MANUFACTURING METHODS AND PROCESSES The second major category of patents and applications covered methods and processes of manufacturing the drugs. There were sixty-eight patents in this category, or 32 percent of the total. The patented methods and processes related to creating analog compounds, or compounds that are similar in structure to ritonavir or lopinavir; intermediate compounds; alternate formulations or compositions; and polymorphs.

METHODS OF TREATMENT OF HIV AND OTHER DISEASES We found thirty-one patents and applications (15 percent of the total) covering the use of ritonavir, lopinavir, or lopinavir/ritonavir in treating patients with HIV infection or other diseases. The key patents in this category were sought and granted after a new use for ritonavir was discovered as a potent inhibitor of the cytochrome-P450 3A4 (CYP3A4) system in humans, which allows the drug to increase the potency of other protease inhibitors. For example, patent number 6,037,157 (which expires in 2016) covers the method of improving the pharmacokinetics of drugs metabolized primarily by the CYP3A4 system by treating the patient with both

ritonavir and one of those drugs.

Twelve of the thirty-one patents in this category (39 percent) claimed applications of ritonavir that were unrelated to managing HIV infection. For example, patent number 7,320,961 claims the method of using ritonavir to treat unconjugated hyperbilirubinemia—which is an increased level of bilirubin in the blood that can be toxic.

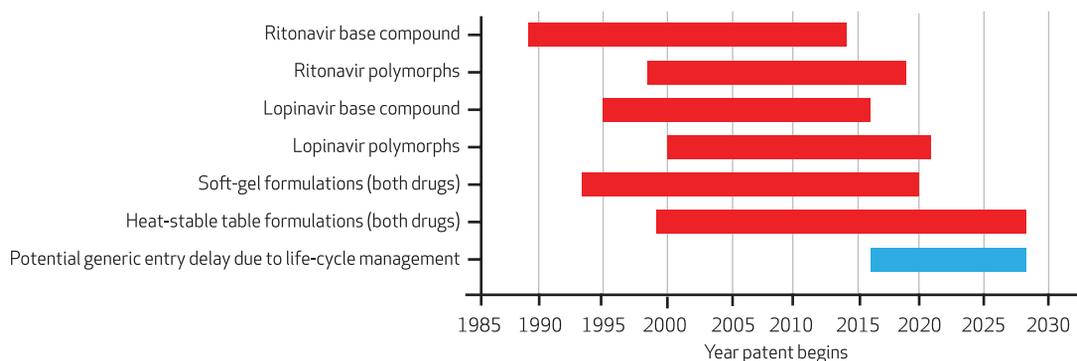
GENERAL PATENTS We found twenty-eight patents and applications held by Abbott covering other compositions or formulations and processes that did not specifically mention either lopinavir or ritonavir but that could still serve as roadblocks to generic competition. This category contained 13 percent of the patents.

Five of them (18 percent of patents in the category) were applications covering general compositions or formulations. Another eleven (39 percent) covered general processes for solid oral dosage formulations.

PATENT-RELATED MARKET EXCLUSIVITY MODEL We used the expiration dates of the patents we identified to build a patent-related market exclusivity model for ritonavir and lopinavir/ritonavir (Exhibit 2). In general, we found that most of the patents extending past the expiration date of patents on the original base compounds fell into the categories of polymorphs (lasting up to 2019 for ritonavir and 2021 for lopinavir); methods of use of the drugs; and formulation patents—in particular, the heat-stable tablet for-

EXHIBIT 2

Duration Of Patents Covering Ritonavir And Lopinavir/Ritonavir



SOURCE Authors' analysis. **NOTES** Timeline represents patents and patent clusters held by Abbott Laboratories. Dates shown are subject to future patent extensions and reexamination of patents at the request of parties who may have evidence of lack of inventiveness. The blue bar represents potential delay in generic entry as a result of life-cycle management, and not a patent duration. Polymorphs are defined in the text.

mulation.

The final patent covering lopinavir/ritonavir that was in force at the time of this study is scheduled to expire in 2028, twelve years after the expiration of the patents on the underlying base compounds. Currently pending applications on the modified heat-stable formulations may extend this expiration date even further.

On further examination, we identified signs of quality concerns—particularly overlapping patenting—among the patents within the four identified categories. For example, we identified nine overlapping patents²³ related to the soft-gel capsule formulation of ritonavir and lopinavir/ritonavir. The earliest of these patents expires in 2013 and the latest in 2020. Although these patents remain in force, the overlapping nature of their subject matter may serve as a basis for challenging their validity in court.

These nine patents also claimed variations of excipients—pharmacologically inactive substances used as a carrier for the active ingredients of a drug—that could be challenged for lacking novelty and for being obvious. For example, patent number 6,911,214 used excipients covered in earlier patents, but with the addition of flavoring systems such as peppermint, vanilla, and cotton candy that would probably be used in the lopinavir/ritonavir oral solution for pediatric use.

Another patent cluster—patent numbers 7,364,752 and 8,025,899 and pending patent application number 2005/0143404—involved the heat-stable tablet version of lopinavir/ritonavir. Nine other pending applications covered variations of the heat-stable formulation technique as well.

These patents also raised potential quality concerns. For example, we found patent number 8,025,899 to be similar to patent number

7,364,752. The latter uses the synthetic water-soluble polymer polyethylene glycol as the key excipient; by contrast, the former uses the synthetic water-soluble polymer polyvinylpyrrolidone. However, pharmaceutical scientists have suggested in earlier scientific articles and patent documents the benefits of using such excipients for formulating pharmaceutical products,^{24,25} which calls into question the nonobviousness of these patents. Indeed, in an earlier 1996 publication, Abbott reported using polyvinylpyrrolidone and other excipients with ritonavir alone for the purposes described in patent numbers 7,364,752 and 8,025,899.²⁶

Similarly, pending application number 2007/0249692 covered a combination of the water-soluble polymers used in patent numbers 7,364,752 and 8,025,899, while two additional applications (numbers 2008/0181948 and 2009/0220596) contained claims similar to those in patent 8,025,899. If approved as written and listed in the *Orange Book*,¹⁷ these various applications could delay a generic drug's entry into the market, extend the expiration date of the currently marketed formulation, or protect a new version of lopinavir/ritonavir that claimed improvements over the current form.

Patents covering polymorphic forms also raised concerns of patent validity. One of the controversies around the patenting of polymorphs is that they are not “invented” but exist in the base chemical compound and are merely discovered as part of compound screening.²⁷ In the case of Abbott's patent on the amorphous form of ritonavir (number 7,148,359), it is notable that a publication from scientists at Abbott discloses that the company had already discovered an amorphous form of ritonavir in 1996.²⁶ If this earlier publication were raised in

Settlements between brand-name and generic manufacturers keep potentially invalid patents in force in exchange for payments to a generic challenger.

a reexamination or post-grant opposition process before the US Patent and Trademark Office, or in litigation in the courts, it could negate the novelty in these subsequent polymorph patents. As a result, the rights obtained through these patents could be revoked.

Discussion

LIFE-CYCLE MANAGEMENT In this study we sought to describe the array of patents held by Abbott that cover two protease inhibitors used widely in the treatment of HIV infection. The 108 patents we identified could extend the market exclusivity of ritonavir and lopinavir/ritonavir to at least 2028—twelve years after the expiration of the patents on their base compounds and thirty-nine years after the first patents on ritonavir were filed.

Our data provide some insight into the practice of life-cycle management. Abbott received or has applied for a complex patchwork of patents covering all aspects of the drug production process. Some of these patents were filed before key patents for the drugs' base compounds were officially listed in the *Orange Book*,¹⁷ which suggests an early start for secondary patenting in the product life cycle.

Because our data were derived from patent searches, we did not have insights into the manufacturer's intent in seeking the patents. The rationale is somewhat obvious for the initial patents on the underlying active ingredient, and even for the patents on updated formulations such as the heat-stable version. Some patents—for example, combination patents protecting ritonavir's use with other drug compounds, such as saquinavir, that are used against HIV—may have been seen as protecting potential future

products.

However, the substantial number of later-issued patents, particularly those related to intermediate compounds and manufacturing processes, force prospective generic entrants to spend considerable time and resources mapping the patent landscape, evaluating the reach and strength of each patent they identify, and possibly seeking to have some patents overturned in court. Such steps make it more difficult and costly to develop and market a generic product once patents on the base compounds have expired.

The concept of life-cycle management has been controversial, in part, because later-issued drug patents may indeed encompass beneficial improvements over a prior version of the drug.^{28,29} For example, the currently marketed heat-stable tablet formulation of ritonavir and lopinavir/ritonavir has no additional therapeutic benefit over the soft-gel version, but it is considered an improvement because it ensures the drug's potency in suboptimal storage conditions and allows patients to take two fewer pills each day.³⁰

However, we found that some of the patents in our analysis were of questionable inventiveness, using techniques and excipients already known in the field. Nevertheless, these are only signals of potential validity questions, not legal conclusions.

POLICY IMPLICATIONS Our exploratory study has important implications for pharmaceutical policy related to drug patents. The burden of cutting through the array of patents surrounding drugs like ritonavir and lopinavir/ritonavir now falls on manufacturers of generic drugs seeking to introduce a competing product.³¹ This process usually involves protracted litigation, which in recent years has also been characterized by settlements between brand-name and generic manufacturers that keep potentially invalid patents in force in exchange for payments to a generic challenger.³² As a result, patients and health insurers continue to pay high prices for drugs long after the initial patents on the underlying base compounds expire.

Alternative options are needed that restrict inappropriate life-cycle management strategies, while not preventing manufacturers from seeking and earning legitimate patents on worthwhile improvements to their drug products. For example, if the US Patent and Trademark Office permitted outside experts to provide opinions about individual patents during the pharmaceutical patent evaluation process, the introduction of duplicative or otherwise invalid patents might be reduced.³³

As a first step in this direction, the Patent Reform Act of 2011 established a postpatent

grant opposition proceeding—known as Post Grant Review—in which third parties can challenge a patent's validity by submitting any additional information bearing on the patentability of the claimed invention. However, once a patent is granted, there is a strong presumption of validity, and generic manufacturers are blocked from production until the patent is ultimately revoked.

We believe that the window of nine months within which to file a Post Grant Review should be extended, because it can sometimes take a few years after a patent is granted before its relevance and importance to a generic producer are known.³² In addition, the projected costs of a post-grant opposition, which could be up to \$339,000, are prohibitive for many potential interveners.³⁴

We further believe that patent opposition procedures would be more effective if there were also an opposition procedure prior to the granting of patents, involving lower petitioning fees so as not to limit potential interveners. This would allow patent applications for new formulation compositions and polymorphs—applications that are common obstacles to the timely market entry of generic drugs—that are not of high quality to be challenged and weeded out ahead of time. Such a measure could help reduce the need for expensive litigation after patents are granted, although managing such cases might require increased resources for the US Patent and Trademark Office.

The current rules under which third parties can submit information before a patent is issued restrict both the amount of information and the way in which the information can be submitted. The US Patent and Trademark Office has sought to improve these rules by increasing the time period within which third parties may submit a patent from two months to six months from date of publication of the patent.³⁵ A pre-grant opposition process also could allow the party submitting the information to participate in the examination of a patent application—for example, by permitting responses to evidence supporting the patent application provided by an applicant.

In addition to an improved pre- and post-grant opposition system, inappropriate patenting practices might be reduced if manufacturers were required to publicly identify all patents relating to a compound, perhaps in a readily accessible online database. Of the 108 patents we identified relating to ritonavir, lopinavir, and lopinavir/ritonavir, only 20 are currently listed in the *Orange Book*.¹⁷ Requiring all patents, including applications, to be listed in a public database would provide greater transparency into

patenting practices and provide generic entrants with a clearer picture of the potential obstacles. The database might be organized along the lines of *ClinicalTrials.gov*, which provides information about ongoing clinical research studies.

Furthermore, the Food and Drug Administration could be permitted to audit the eligibility of patents listed in the *Orange Book*,¹⁷ based on information received by third parties. Patents are listed in the *Orange Book* for the purpose of informing potential competitors about the relevant patents protecting the brand-name version of a marketed product that would need to be overcome and about their expiration dates, only after which can approval of a generic equivalent be granted.

This would be similar to the current practice in Canada. Health Canada's Office of Patented Medicines and Liaison accepts information on the eligibility of a listed patent, including its validity, from interested parties. If a patent is alleged to be improperly listed, the office will undertake a review of the patent and may delist it.³⁶

Of course, the most effective method to counteract inappropriate extensions of market exclusivity resulting from improper life-cycle management would be to raise the bar for patentability. For instance, the threshold for non-obviousness could be raised. A number of developing countries—including Argentina, India, and the Philippines—have introduced more stringent patentability standards that make polymorphs, formulations, and additional uses of existing compounds more difficult to patent.

In India, for example, patents claiming improvements over existing compounds currently need to provide evidence of added clinical benefit. This requirement, along with higher standards of proof required to show that inventions are not obvious, has resulted in the subsequent rejection by the Indian Patent Office or voluntary withdrawal by Abbott of several of the US patents identified in this study. In part as a result, generic versions of lopinavir/ritonavir are already available in India.

In the United States, a 2007 Supreme Court case redefined one aspect of the test for non-obviousness. The case, *KSR International v. Teleflex*, concerned a patent on the combination of an adjustable vehicle control pedal with an electronic throttle control.³⁷ In ruling that the combination of the two elements was unpatentable, the Supreme Court opted for a more expansive and flexible approach to nonobviousness, which could make invalidating a patent less difficult. Although the case did not relate to a drug, it could have relevance to future cases of pharmaceutical combination products, such as lopina-

vir/ritonavir.

Firmer statements about standards for non-obviousness by the US Patent and Trademark Office or the courts, specifically addressing aspects of pharmaceutical chemistry such as polymorphs or new formulations, are needed to help

ensure that only true innovations in this field are protected by twenty-year market exclusivity, and that changes based on common pharmacological experimentation and knowledge are not similarly rewarded. ■

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does not take funding from generic or originator pharmaceutical companies. On a pro bono basis on behalf of low-income patients living with HIV, I-MAK has filed pre-grant oppositions and observations against Abbott Laboratories' patents for ritonavir, lopinavir, and lopinavir/ritonavir in India and at the European Patent Office.

I-MAK selectively intervenes in drug patent cases where patentability criteria are clearly not met. The authors thank Joseph Fortunak, a pharmaceutical scientist, for his help in evaluating the patents; Priti Radhakrishnan for her comments on earlier drafts; and Sabrina Mawani for assisting with research and patent searches.

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Tahir Amin is cofounder and director of intellectual property at I-MAK.

In this month's *Health Affairs*, Tahir Amin and Aaron Kesselheim report on their study of how securing so-called secondary patents on drugs—for features other than the original active ingredient—can effectively extend market exclusivity for medications and prevent timely introduction of generics into the market. Examining two antiretroviral drugs for HIV, they identified 108 patents that could delay generic competition for decades after the drugs' first patents were filed. The authors argue for a series of policy changes that would limit secondary patents and open the door to lower-cost generics at a more appropriate time.

Amin is cofounder and director of intellectual property at the Initiative for Medicines, Access, and Knowledge (I-MAK), a team of lawyers and scientists focused on

increasing access to affordable medicines through improvements to the patent system. He is also a practicing solicitor in the Senior Courts of England and Wales and a fellow in the Department of Global Health and Social Medicine at Harvard Medical School.

Amin has extensive experience in patent and trademark law. Prior to founding I-MAK, he researched public interest intellectual property issues and worked on pharmaceutical patent oppositions in India and Europe. He has served as a legal adviser or consultant to organizations such as the World Health Organization, UNITAID, and the Clinton Health Access Initiative. Amin received a law degree and a postgraduate diploma in legal practice from the University of Westminster, in London.



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Kesselheim is board certified in internal medicine and a member of the New York bar. In 2010 he received the Alice S. Hersh New Investigator Award from AcademyHealth. Kesselheim earned a master's degree in public health from the Harvard School of Public Health and medical and law degrees from the University of Pennsylvania.

Additional Details on Patent Identification Methods

Patent searching

We first identified US patents and patent applications protecting ritonavir, lopinavir, and ritonavir/lopinavir in combination. We included patent applications because nearly all patent applications in the pharmaceutical sciences are ultimately granted,¹ and the period of market exclusivity starts from the date of application. Ritonavir (Norvir) was sponsored by Abbott Laboratories and approved by the Food and Drug Administration (FDA) in 1996, and Abbott's Kaletra (lopinavir/ritonavir) was approved in 2000. Lopinavir has never been approved as a single-entity product in the US.

As a data source, we used the Thomson Innovation comprehensive database of US patent applications and granted patents.² This database is searchable based on terms of interest within certain sections of the patent document, including the title, inventor (the person responsible for creating the intellectual property), assignee (the person or company, if any, that owns the inventor's patent rights), abstract (short description), claims (list of items on which the applicant seeks

exclusive rights), and description (a longer explanation of the invention and its function).

Our detailed search process has been described elsewhere.³ To ensure the broadest possible results, we conducted 10 different searches of the Thomson database using specific key terms in each of these patent subfields that are commonly associated with ritonavir, lopinavir and ritonavir/lopinavir (**Appendix Table 1**). Since these drugs are members of the protease inhibitor class (also referred to as retroviral protease inhibitors), the key descriptive terms we used were "protease", "inhibiting", and "retroviral". We included "Abbott" in the assignee subfield of each query. Search terms were linked with the Boolean operator "AND".

From this first search process, we extracted the names of all inventors associated with Abbott listed on a ritonavir, lopinavir or combination patent and conducted a second round of searches that included the inventors' names alongside Abbott (as the assignee). This supplemental search was intended to identify additional patents originating from Abbott's employees/vendors claiming processes of drug production or delivery, such as general solid dispersion formulations, that might not mention the names of the drugs or the drug class specifically. We then combined of the results from these two search strategies. Patent searches were conducted up

to April 2011, with final status checks of patents identified carried out in December 2011.

Patent selection

From our initial list, we first removed all duplicates. We then analyzed each patent or patent application to extract the subject matter. We included any patent or application that claimed any pharmaceutical component of ritonavir, lopinavir or ritonavir/lopinavir, or any product related to these compounds. Finally, we cross-checked the search results to ensure they included specific patents listed by Abbott in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book).⁴ Further double-checking was conducted by querying the INPADOC patent families through the esp@cenet database⁵ and the backward and forward citations for each of the identified patents using Thomson Innovation and esp@cenet. These searches identified no additional relevant patents for inclusion in our final cohort.

Appendix Table 1. Patent review search terms and strategy

Search	Assignee/Applicant	Title	Abstract	Claims	Description
1	Abbott				Protease
2	Abbott	Protease	Protease	Protease	
3	Abbott				Retroviral
4	Abbott	Retroviral	Retroviral	Retroviral	
5	Abbott	Retroviral AND Protease	Retroviral AND Protease	Retroviral AND Protease	Retroviral AND Protease
6	Abbott	Protease AND Inhibiting	Protease AND Inhibiting	Protease AND Inhibiting	Protease AND Inhibiting
7	Abbott				Ritonavir
8	Abbott	Ritonavir	Ritonavir	Ritonavir	
9	Abbott				Lopinavir
10	Abbott	Lopinavir	Lopinavir	Lopinavir	

Notes: Assignee/Applicant=the owner of the patent rights; Title=the title of the patent; Abstract=summary of the patent document; Claims=the inventions; Description=full explanation of the invention and the mechanism

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