MAKE BETTER DECISIONS

FINDING AND EVALUATING GENERIC AND BRANDED DRUG MARKET ENTRY OPPORTUNITIES

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DRUGPATENTWATCH.COM

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About DrugPatentWatch

DrugPatentWatch is a provider of global business intelligence on biologic and small-molecule drugs, dedicated to helping clients make better decisions.

Critical information on global drug patents is incorporated with litigation intelligence, drug prices, and historic sales figures to help users discover commercial opportunities and forecast future revenue events. Since 2005 DrugPatentWatch has served hundreds of large and small companies in more than 65 countries.

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About the Author

Yali Friedman, Ph.D. is the founder and publisher of DrugPatentWatch.

Dr. Friedman is also publisher of the *Journal of Commercial Biotechnology* and author of *Building Biotechnology*, which is used as a course text in dozens of biotechnology programs. He was also named one of the 100 most influential people in biotechnology by *Scientific American.*

Dr. Friedman has strong exposure to leading issues in international drug development. Over the span of ten years he developed and maintained the *Scientific American worldVIEW* scorecard, a global biotechnology perspective profiling biotechnology industries and innovation capacity in dozens of countries, and he has been invited to participate in biotechnology industry development forums for international groups such as APEC, in Europe, and throughout Asia.

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This book is not a substitute for advice from an attorney. If you require legal or other expert advice you should seek guidance from a suitable and competent attorney or other expert.

Reasonable efforts have been made to ensure the accuracy of this book. However, there may be mistakes or omissions. Further, patents, laws, economic conditions, and their interpretations are constantly changing. Accordingly, this book should only be used as a general guide. It is not appropriate to use this book as an independent source.

Dedication

I am grateful to all the DrugPatentWatch clients I have had the opportunity to serve. I have been privileged to bear witness to the changing needs of stakeholders at the bleeding edge of innovative and generic drug development and healthcare delivery. Thank you all for your questions.

I am also indebted to my very patient wife. She was, in a sense, the first to "read" this book, as she (repeatedly) listened to me describe all the challenges, opportunities, and nuances of drug development and the intricacies of legal and regulatory influences. And, beyond simply passively listening, she has challenged me to dig deeper and to explain better. I thank you, Suzanne, for your patience and for your questions.

Introduction

This book is the product of more than twenty years of providing guidance to drug development companies and other healthcare stakeholders. Through developing the first website on the business of biotechnology in the 1990s (now owned by the *New York Times*), editing and publishing the *Journal of Commercial Biotechnology*, and leading data analytics for a subsidiary of *Scientific American*, I have had the fortune of spending considerable time at the bleeding edge of the commercial side of drug development.

The motivation to write *Make Better Decisions* comes from my experiences running DrugPatentWatch, a comprehensive platform to help identify and evaluate opportunities around drug patent expiration and generic entry. The first version of DrugPatentWatch was developed in response to repeated requests to answer the simple question: "When do drug patents expire?" As the platform matured, it became apparent that there was a strong need for a single source integrating broad strategic guidance to help stakeholders throughout the drug development and delivery value chain. *Make Better Decisions* is written to meet that need.

As with my other publications, the focus of *Make Better Decisions* is on actionable intelligence. Because the legal and regulatory underpinnings of drug development and delivery are complex and change frequently, the approach taken by this book is to explain the current state of affairs and to provide representative examples to help you develop a deep understanding so you can quickly adapt to and capitalize on future events.

A primary objective of this book is to fill gaps in knowledge, helping you leverage your expertise, without being overly exhaustive. I have kept the citations brief and opted to incorporate them in the text rather than as footnotes or endnotes. For readers seeking

greater technical depth I have listed some of the books and web-based resources that I found helpful.

Because strategic planning for branded drugs has many similarities to finding and prioritizing generic entry opportunities, this book has relevance for generic and branded companies alike. Likewise, distributors, payers, investors, and myriad other stakeholders will also benefit by understanding the commercial dynamics of pharmaceutical and biotechnology drugs. I hope you enjoy reading the book as much as I did writing it.

Case Study: Identifying First Generic Entrants

When patents and regulatory protections expire, the market for generic entry is open. But, generics can enter prior to anticipated patent expiration dates if they can work around patents or invalidate them.

Although the Food and Drug Administration (FDA) does not provide information on the identities of companies that file generic drug applications, there are ways to proactively identify generic entrants before they launch. This information is important for many parties. For examples, payers need to know who the first generic entrants will be to adjust their co-payment tiers, to establish substitution rules in advance of generic entry, and to ensure that their budgetary estimates are aligned with market conditions. Likewise, wholesalers and distributors can use knowledge of impending generic entry to avoid overstock of branded drugs and to establish contracts for generic drugs.

Branded and generic firms need to be aware of generic entrants so they can make informed decisions based on historic knowledge of drug pricing strategies, market entry approaches, and opportunities for competition.

Starting With Patent Challenges

Patent challenges are an important part of tracking generic entry. If a generic drug company can successfully invalidate a patent or prove that their drug doesn't infringe on branded drug patents, then they can launch well before patent expiration dates.

In the U.S. patent challenges are formalized through the Paragraph IV certification process (see Figure 1). Tracking Paragraph IV challenges is a quick and effective way to anticipate generic entry in advance of patent expiration dates.

Paragraph IV (Patent) Challenges for VIMPAT

DRUGNAME	DOSAGE	STRENGTH	RLD	DATE
lacosamide	Injection	10 mg/mL, 20 mL	Vimpat	2016-06-30
lacosamide	Tablets	50 mg, 100 mg, 150 mg, and 200 mg	Vimpat	2012-10-29
lacosamide	Oral Solution	10 mg/mL	Vimpat	2012-10-29

Figure 1: Paragraph IV Certifications for Vimpat. ***Source: DrugPatentWatch***

A limitation of tracking Paragraph IV certifications is that while they can help anticipate early generic entry opportunities, they do not name the potential first generic entrant. Because the FDA does not disclose the names of companies filing Paragraph IV certifications, nor the contents of drug applications, it is not possible to directly ascertain the name of the Paragraph IV patent challenger.

Tentative Approvals

Tentative approvals are clearances for drugs to be marketed, but for the existence of patents or market exclusivities. According to the FDA:

> If a generic drug product is ready for approval before the expiration of any patents or exclusivities accorded to the reference listed drug product, FDA issues a tentative approval letter to the applicant. The tentative approval letter details the circumstances associated with the tentative approval. FDA delays final approval of

> the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product.

Because successful Paragraph IV challengers often want to launch as soon as possible following a successful outcome (and, potentially to demonstrate confidence in the strength of their case), they will often obtain tentative approvals for the drugs for which they have launched patent challenges. So, looking at the recent tentative approvals (see Figure 2) can provide an indication of who the Paragraph IV filer may be.

Generic filers with tentative approvals for LACOSAMIDE

Applicant	Application No.	Strength	Dosage Form
Glenmark Pharms Ltd	204980	10MG/ML	SOLUTION;ORAL
Glenmark Pharms Ltd	205006	150MG	TABLET;ORAL

Figure 2: Tentative approvals for Lacosamide. *Source: DrugPatentWatch*

Note: an added feature of tentative approvals is that drugs being distributed under the President's Emergency Plan for AIDS Relief (PEPFAR) must either have traditional FDA approval, or a tentative approval. Therefore tentative approvals can, even in the absence of impending patent expiration or invalidation, provide market entry opportunities.

Patent Litigation

There are two methods of challenging patents in the U.S. Regardless of the method used to challenge a patent, the parties involved will be named and the proceedings will be made public, so examining the litigants can identify the Paragraph IV filer, and therefore the first potential generic entrant.

The older, and more comprehensive, method is conventional litigation in district courts (see Figure 3). Generic companies must send branded companies a notice of their Paragraph IV certification within 20 days of confirmation of ANDA receipt by the FDA, and branded firms have 45 from receipt of the notice letter to file a patent infringement lawsuit and gain an automatic 30-month stay on ANDA approval. District court litigation is where branded company infringement cases will be brought, so looking at the defendants in these cases can identify Paragraph IV filers.


US Court Litigation for CUBICIN

Glossary

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PATENT	CASE NAME	DOCKET	DATE FILED	DATE TERMINATED	CAUSE	COURT	JURY DEMAND	LINK TO DOCKET
8,466,967	Cubist Pharmaceuticals LLC v. Crane Pharmaceuticals LLC	1:16-cv-00012	2016-02-10		35:271 Patent Infringement	District Court, D. Delaware	None	External link to docket
8,852,689	Cubist Pharmaceuticals LLC v. Crane Pharmaceuticals LLC	1:16-cv-00072	2016-02-10		35:271 Patent Infringement	District Court, D. Delaware	None	External link to docket
8,466,967	Cubist Pharmaceuticals LLC v. Sagent Pharmaceuticals, Inc.	1:15-cv-01164	2015-12-17		35:271 Patent Infringement	District Court, D. Delaware	None	External link to docket

Figure 3: Cubicin patent infringement litigation. *Source: DrugPatentWatch*

Generic companies can also launch patent validity challenges before the Patent Trial and Appeal Board (See Figure 4). These challenges are not eligible for 180-day generic market exclusivity so they are not frequently used by Paragraph IV filers, but they can be effective sources of identifying potential generic entrants not using the Paragraph IV certification pathway.

Patent Trial and Appeal Board Cases for ACZONE

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PATENT	PETITIONER	STATUS	FILING DATE	ACCORDED FILING DATE	PATENT OWNER	TRIAL TYPE	TRIAL NUMBER	DECISION DATE	INVENTOR	DOCUMENT DOWNLOAD
9,517,219	Mylan Pharmaceuticals Inc.	Notice Of Filing Date Accorded	2019-06-07	2019-06-07	Warner et al	Inter partes review	IPR2019-01095			Download case documents from USPTO
9,517,219	Amneal Pharmaceuticals LLC	Instituted	2018-11-06	2018-11-06	Warner et al	Inter partes review	IPR2019-00207	2019-05-10		Download case documents from USPTO

Figure 4: PTAB cases for Aczone. *Source: DrugPatentWatch*

Press Releases and Public Disclosures

Another approach is to examine press releases mentioning the drug for which a patent challenge has been filed.

Publicly-traded companies are required to promptly publicly disclose many types of information, and this means that challengers and defendants in patent invalidity suits will often be compelled to disclose the existence of patent litigation, along with the names of the parties involved. So even if only one party is publicly-traded, their disclosures can still name the other party.

Figure 5 shows a filing from BioDelivery Sciences disclosing that Actavis had filed an ANDA with a Paragraph IV certification. Note that they refer to receipt of a *purported* notice; successfully disputing the validity of a notice letter can derail a Paragraph IV certification.

Item 8.01Other Events

On February 8, 2016, BioDelivery Sciences International, Inc. (the "Company") received a purported notice relating to a paragraph IV certification from Actavis Laboratories UT, Inc. ("Actavis") seeking to find invalid three Orange Book listed patents of the Company (the "Patents") relating specifically to the Company's BUNAVAIL® buccal film for the maintenance treatment of opioid dependence. The paragraph IV certification relates to an Abbreviated New Drug Application (the "ANDA") filed by Actavis with the U.S Food and Drug Administration ("FDA") for a generic formulation of BUNAVAIL. The Patents subject to Acatvis' certification (which relate to the Company's BEMA® film delivery technology) are U.S. Patent Nos. 7,579,019 ("the '019 Patent"), 8,147,866 and 8,703,177.

The Company believes that Actavis' claims of invalidity of the Patents are wholly without merit and, as it has done in the past, the Company intends to vigorously defend its intellectual property. The Company is highly confident that the Patents are valid, as evidenced in part by the

Figure 5: Company filing disclosure identifies Paragraph IV filer. ***Source: U.S. Securities and Exchange Commission***

Additionally, even private companies (not subject to the same disclosure requirements as publicly-traded companies) have an incentive to announce Paragraph IV certifications. Issuing press releases announcing their patent challenges can help establish distribution and supply-chain relationships in anticipation of generic launch.

Case Study: Viagra Generic Entry

The story of Viagra's patents and the generic entry of sildenafil citrate is a valuable one because it covers many of the nuances of drug patenting and generic entry in the U.S.

Pfizer used multiple patents, a Hatch-Waxman patent term extension, a pediatric extension, litigation, an out-of-court settlement, and an authorized generic fighter brand to protect the market for Viagra.

Viagra was approved in 1998, and the original patent covering Viagra was 5,250,534. This patent received a 283-day Hatch-Waxman patent term extension giving it an expiration date of March 29th, 2012. This 14-year patent life is longer than for many other drugs, but Pfizer was able extend the patent-protected life even further.

Patent 5,250,534 was filed in 1990, and in 1994 (four years prior to Viagra's launch) Pfizer filed a second patent: 6,469,012. Because patent 6,469,012 was filed prior to June 8th 1995, its term is *17 years from the grant date*, rather than *20 years from the filing date*, which is how expiration is determined for patents filed after Jun 8th 1995.

Patent 6,469,012 was granted on October 22nd, 2002, so the original expiration date was set to October 22nd, 2019 â€" more than twenty years after the drug's launch. The patent's expiration was extended to April 22nd, 2020 because Pfizer responded to an FDA request to perform pediatric clinical trials, granting six months of *pediatric exclusivity* protection.

Patent Challenges and Out of Court Settlement

Pfizer successfully defended Viagra's patents in many patent litigations, but one lawsuit stands out. Despite prevailing in a lawsuit against Teva which affirmed the validity of patent 6,469,012, in 2013 Pfizer announced an out-of-court settlement with Teva, granting Teva a license to manufacture and sell generic sildenafil citrate starting in December 2017, more than two years before Viagra's patent expiration. Importantly, this was not a "reverse-payment" patent settlement, as rather than simply delaying their launch in exchange for payment Teva was required to pay Pfizer a licensing fee to produce the generic.

Launching an Authorized Generic to Fight Generic Entry

Generic drugs sell at a discount to the branded version, which hurts branded revenues, but there are things which brands can do to limit the impact. A popular tactic is to launch an authorized generic. In this strategy a branded firm licenses a third party to market the branded drug under another name, compelling the generic entrant (in this case Teva) to compete in the generic market. The authorized generic for Viagra was Revatio and it was licensed to several suppliers (see Figure 1).

REVATIO

Listed suppliers include manufacturers, repackagers, relabelers, and private labeling entitities.

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APPLICANT	TRADENAME	GENERIC NAME	DOSAGE	NDA	NDA/ANDA	SUPPLIER	PACKAGE CODE	PACKAGE
Pfizer	REVATIO	sildenafil citrate	TABLET;ORAL	021845	NDA AUTHORIZED GENERIC	Greenstone LLC	59762-0033-1	90 TABLET, FILM COATED in 1 BOTTLE (59762-0033-1)
Pfizer	REVATIO	sildenafil citrate	TABLET;ORAL	021845	NDA AUTHORIZED GENERIC	Aphena Pharma Solutions - Tennessee, LLC	43353-345-53	60 TABLET, FILM COATED in 1 BOTTLE (43353-345-53)
Pfizer	REVATIO	sildenafil citrate	TABLET;ORAL	021845	NDA AUTHORIZED GENERIC	Aphena Pharma Solutions - Tennessee, LLC	43353-345-20	20 TABLET, FILM COATED in 1 BOTTLE (43353-345-20)

Figure 1: Revatio suppliers

Lessons for Predicting Generic Entry

The story of Viagra and the generic entry of sildenafil citrate illustrates the value of patent and litigation data and the need to continuously re-evaluate factors affecting generic entry. Reliance on the first patent would have vastly under-estimated the date of generic entry, and looking solely at the expiration date of the second patent would have missed the December 2017 generic entry.

Case Study: Extracting Competitive Intelligence From Litigation

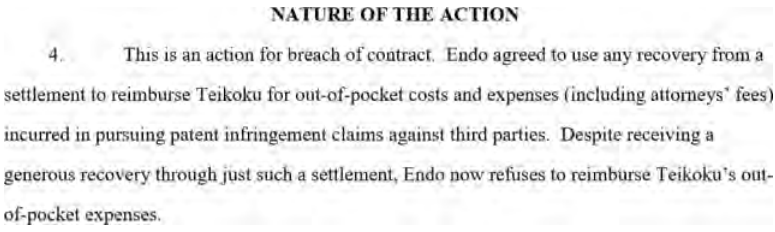
Many kinds of competitive and business intelligence can be obtained by studying litigation.

For example, a company seeking to license a drug to, or from, another party may want to know what terms the other party has agreed to in other instances. The specific terms of agreements between companies are generally not disclosed, but they may become available should a court case necessitate their mention.

When facing patent litigation it can be very useful to know how aggressive the other party is, and also what settlement terms they may accept.

When parties agree to a out-of-court settlement *in lieu* of continuing with litigation the terms of the settlement are generally not publicly disclosed. But, subsequent lawsuits can reveal the terms of a settlement. This knowledge can be used in future litigation to predict what terms a party may find acceptable in an out-of-court settlement.

The case of *Teikoku Pharma USA, Inc. v. Endo Pharmaceuticals, Inc.* illustrates how information about an out-of-court settlement can be revealed in subsequent litigation. In this case Teikoku asserted that they had an agreement with Endo in which Endo would reimburse Teikoku for expenses incurred in pursuing patent infringement claims against third parties, and that Endo had failed to satisfy the terms of that agreement (see Figure 1).



NATURE OF THE ACTION

4. This is an action for breach of contract. Endo agreed to use any recovery from a settlement to reimburse Teikoku for out-of-pocket costs and expenses (including attorneys' fees) incurred in pursuing patent infringement claims against third parties. Despite receiving a generous recovery through just such a settlement, Endo now refuses to reimburse Teikoku's out-of-pocket expenses.

Figure 1: Teikoku sues Endo for patent litigation expenses. ***Source: *U.S. Courts***

If true, the *Nature of the Action* reveals firstly that future partners may want to consider asking for Endo to cover litigation expenses. For it appears that Endo is willing to accommodate these terms in their partnership agreements. It is also worth noting that partners with Endo who have expense-recovery clauses in their agreements should review the full proceedings of the litigation to ascertain the merits of the complaint and gauge the likelihood of receiving compensation for pursuing patent infringers.

How Much Will a Company Spend to Pursue Patent Infringers?

The risk of being sued for patent infringement is a persistent concern among generic companies. Even in cases where generic firms are confident that they are not infringing any patents there remains the risk that a patent holder will view the situation differently and pursue legal action. So, an important consideration in launching generic drugs is to evaluate the strength of cases which may be brought by patent owners, and the resources which the patent owners may dedicate to challenging infringers.

Figure 2 provides key insights into Teikoku's tactics in pursuing perceived patent infringers. Firstly, they spent $2.3 million in litigation against Watson, and secondly they entered into a settlement agreement to resolve the dispute. A deeper look into Teikoku's litigation with Watson could yield additional insights into the other tactics employed by Teikoku.

21. On May 28, 2012, after post-trial briefing, but before the trial court had issued a decision on the merits, the parties entered into a Settlement and License Agreement (the "Settlement Agreement").

22. As of that date, Teikoku incurred in the Watson Litigation unreimbursed out-of-pocket costs and expenses (including attorneys' fees) of $2,313,496.99.

23. Through the Settlement Agreement, Endo and Teikoku agreed to release the claims they had asserted against Watson in the Watson Litigation and to other consideration. In return, among other things, Watson agreed to pay Endo a royalty equal to 25% of all gross profits enjoyed by Watson from the sale of generic Lidoderm® for a defined period of time. At the time the parties executed the Settlement Agreement, it was uncertain whether Watson would ever make any royalty payments to Endo as Watson's proposed generic product had not, at that time, been approved by the FDA.

Figure 2: Legal expenses and settlement terms. ***Source: *U.S. Courts***

As demonstrated in this case, companies being challenged by Teikoku for patent infringement may anticipate that Teikoku will spend at least $2.3 million on their prosecution of the case. Further, should a defendant elect to offer a settlement they may believe that Teikoku will accept a royalty of 25% of gross profits. Conversely, plaintiffs asserting patents against Watson may expect that Watson will agree to pay a 25% royalty to resolve the litigation.

How Much was Earned in Royalties?

In addition to extracting the terms of Teikoku's partnership terms with Endo, and further learning about Teikoku's tactics in pursuing perceived infringers, it is still possible to learn more from this case.

Teikoku's assertions in Figure 3 claim that Endo earned over $100mm in license fees from Watson over the roughly 21 month timespan cited. Back-calculating from the 25% royalty rate over nearly two years, it would appear that Watson's sales were over $200mm/year.

25. From September 15, 2013 to the present, Endo received royalty payments from Watson of over $100 million, an amount substantially exceeding the combined expenses incurred by Endo and Teikoku in bringing the Watson Litigation. These royalty payments constitute a "recovery obtained as a result of the Suit" as that term in used in the Letter Agreement.

26. Although Teikoku has demanded reimbursement of the expenses it incurred in bringing the suit, Endo has refused to so reimburse Teikoku.

Figure 3: Royalty payments received. ***Source: *U.S. Courts***

Beyond learning about Endo's royalty earnings or Watson's revenues from generic drug sales, tactical information can also be gleaned from this case. For example, generic companies often have base parameters which define which opportunities they will pursue. From this case it would appear that Watson finds a $200mm/year revenue projection attractive when deciding to develop a generic drug.