

# How Drug Life-Cycle Management Patent Strategies May Impact Formulary Management

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*This article is based on discussions from a recent roundtable meeting that focused on how drug life-cycle management patent strategies affect the decision-making process regarding formulary planning and management strategies when single-source, branded oral pharmaceutical products transition from single-source to generic status in the United States. The roundtable participants also explored several strategies manufacturers employ to extend marketing exclusivity. The panel was moderated by Jan Berger, MD, MJ.*

**S**peeding access to generic medications is a pillar of pharmacy benefit management, as well as a key systematic way of managing pharmaceutical cost trends. The small-molecule blockbuster medications have in recent years entered a “patent cliff,” wherein a significant number of generic drugs has begun to enter the marketplace. This wave has increased competition and yielded significant cost savings for a number of stakeholders. Several important small-molecule drugs have US patent expirations slated for 2016, including Benicar (olmesartan medoxomil), Benicar HCT (olmesartan medoxomil and hydrochlorothiazide), Crestor (rosuvastatin calcium), Cubicin (daptomycin), Zetia (ezetimibe),<sup>1</sup> and perhaps, although unlikely, Zytiga (abiraterone acetate), as will be discussed later in this article. Health plans, insurers, and pharmacy benefit managers (PBMs) add generics to their drug formularies as quickly as possible to benefit from savings versus comparator branded medications.

When developing a medicine to bring to the market, a pharmaceutical company may spend up to \$2.6 billion (in 2013 US dollars)<sup>2</sup> to identify a compound and complete the necessary preclinical and clinical trials to file a new drug application (NDA) with the FDA. This investment results in precious intellectual property that can bring in revenue for a drug maker for years to come. Without protection of this intellectual property, the pharmaceutical industry would be reluctant to invest the capital needed to develop innovative new products to improve health for individual patients and populations.

In recent years, an increased amount of attention has been paid to pharmaceutical patents and litigation in the press and with payers.<sup>3</sup> With the increased attention on pharmaceutical patents, there

## ABSTRACT

*Drug manufacturers may employ various life-cycle management patent strategies, which may impact managed care decision making regarding formulary planning and management strategies when single-source, branded oral pharmaceutical products move to generic status. Passage of the Hatch-Waxman Act enabled more rapid access to generic medications through the abbreviated new drug application process. Patent expirations of small-molecule medications and approvals of generic versions have led to substantial cost savings for health plans, government programs, insurers, pharmacy benefits managers, and their customers. However, considering that the cost of developing a single medication is estimated at \$2.6 billion (2013 dollars), pharmaceutical patent protection enables companies to recoup investments, creating an incentive for innovation. Under current law, patent protection holds for 20 years from time of patent filing, although much of this time is spent in product development and regulatory review, leaving an effective remaining patent life of 7 to 10 years at the time of approval. To extend the product life cycle, drug manufacturers may develop variations of originator products and file for patents on isomers, metabolites, prodrugs, new drug formulations (eg, extended-release versions), and fixed-dose combinations. These additional patents and the complexities surrounding the timing of generic availability create challenges for managed care stakeholders attempting to gauge when generics may enter the market. An understanding of pharmaceutical patents and how intellectual property protection may be extended would benefit managed care stakeholders and help inform decisions regarding benefit management.*

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For author information and disclosures, see end of text.

is a need for better understanding of the relationship between patents and exclusivity, along with the balance between protecting innovation and promoting access to less costly medications. These factors affect pharmaceutical life-cycle management, the transition of products from single-source to multisource status, as well as formulary decision making and pharmacy budget planning.

## The Patent System

Pharmaceutical intellectual property is protected primarily through the US patent system. In the most basic case, a pharmaceutical patent is sought for the creation of a new molecular entity (a “composition-of-matter” patent). The manufacturer applies to the US Patent and Trademark Office (USPTO), which reviews the patent application and makes a decision regarding approval or rejection.<sup>4</sup> Patents can be filed to protect, not only the molecule itself, but the process used to manufacture the drug, how the drug is used, and new formulations of the drug.

All patents on branded pharmaceutical products are registered and listed in an addendum to the FDA-published *Orange Book*.<sup>5</sup> In most cases, the patent is issued by the USPTO an average of 3.4 years after filing for a conventional drug and 4.4 years after filing for a biologic.<sup>6</sup>

According to statute, the granting of a pharmaceutical patent includes protection on that patent for a period of 20 years from time of patent filing. Patent protection may be extended beyond 20 years, depending on whether the processing and review of the patent application was delayed at the patent office or delays were incurred during product review by the FDA.<sup>7</sup>

During the 20-year life of the patent, other drug manufacturers may not sell generic alternatives of the product without the risk of lawsuit and substantial court-approved penalties. In practice, much of the initial 20 years of exclusivity may be spent in product development and regulatory review. The remaining years of patent protection, and the market exclusivity that results, provide economic incentives and considerable potential revenue for a drug company, revenue that is critical to its ability to recover the capital it invests in research and development (R&D) and turn a profit. Most companies also reinvest a substantial portion of revenue back into R&D, so revenue is essential to the development of future drug therapies. The results of a survey by the Pharmaceutical Research and Manufacturers of America indicated that member companies spent 18.6% of total sales on R&D in 2014.<sup>8</sup>

## Product Patents Versus Marketing Exclusivity

Patents and exclusivity work in a similar fashion, but are different from one another. Marketing exclusivity interacts to some extent with patent laws. It is granted through regulatory action by the FDA and guided by statute (the Federal Food, Drug, and Cosmetic Act and the Hatch-Waxman Act). Exclusive marketing rights are granted by the FDA upon approval of a drug, and this

period of marketing exclusivity may or may not run concurrently with the period of patent protection.

In its essence, regulatory exclusivity is a congressionally mandated monopoly under the law. It allows a brand name manufacturer a certain guaranteed period of protection, regardless of what patents they may or may not have. The protection provided by patents, however, is not guaranteed, as discussed later.

Before passage of the Hatch-Waxman Act in 1984 (also known as the Drug Price Competition and Patent Term Restoration Act of 1984 [Public Law 98-417]), the US patent system was the sole protector of intellectual property. Marketing exclusivity was granted to the patent holder, but a finite period after which marketing exclusivity would expire was not defined. Manufacturers who were interested in developing generic drugs had to face the same battery of clinical testing required by the FDA of manufacturers of new chemical entities.<sup>7</sup>

For manufacturers of branded drugs, one problem with the system before 1984 was that the patents could be found to be invalid or unenforceable. Marketing or regulatory exclusivity may be a stronger shield to protect intellectual property. However, legislative and regulatory efforts have not been used solely to protect intellectual property; generally, the intention of these statutes has been to balance patent protection with beneficial access to high-quality, affordable medicines (ie, generics), with the additional result being a period of market exclusivity.

## Hatch-Waxman Act Basics

The Hatch-Waxman Act of 1984 sought to speed access to generic medications by providing generic manufacturers with incentives and a pathway for approval. Hatch-Waxman also provided innovators with meaningful patent protection and an opportunity to recoup their investment, and also provided incentives to generic manufacturers to promote the rapid availability of generic alternatives.<sup>9</sup>

The Act established regulatory exclusivity periods for branded and first generic agents. Exclusivity periods were included in the Act as a lever to promote a balance between new drug innovation and generic drug competition. For example, the first generic manufacturer to challenge a patent for a branded product listed in the *Orange Book* is awarded a 180-day exclusivity period, beginning at FDA approval.<sup>7</sup>

One of the main objectives of the Hatch-Waxman legislation was to promulgate a formal pathway for the introduction of generic drugs, in an effort to bring generics to the market sooner. To achieve this, the Act introduced the abbreviated new drug application (ANDA) process, and detailed the studies and data required by the FDA to evaluate a generic drug for approval.<sup>7</sup>

Under Hatch-Waxman, upon approval of a new chemical entity, the FDA grants a regulatory exclusivity period of 5 years (regardless of patent life remaining). Importantly, as some agents take a longer time to obtain FDA approval, the Hatch-Waxman

Act provides patent-term extensions for those products where a longer time is required by the FDA to review the drug application.<sup>7</sup>

Patents can be filed and granted by the USPTO anywhere along the development life cycle of a drug. Some patent approvals may indirectly extend market exclusivity of a product.

The *Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations)*<sup>8</sup> is published by the FDA. It lists prescription drug products and over-the-counter agents that are approved by the FDA as safe and effective. Manufacturers of branded products must identify USPTO-approved relevant patents and provide information on them, including patent expiration dates, to the FDA, which then publishes this information in the *Orange Book*.

### Generic Drug Approval, Patents, and Exclusivity

A generic manufacturer can bring their drug to market in 2 ways: (1) it can file for approval, and if approved, launch after the branded product's patents and exclusivity period expire, or (2) it can challenge the validity of the branded manufacturer's patent. The latter usually occurs through the litigation process.

The process for challenging a patent listed in the *Orange Book* generally occurs in the following steps:

1. The generic manufacturer submits an ANDA application to the FDA (including their certifying non-infringement of originator's patents).
2. A notice letter is sent to the patent holder. When a generic manufacturer files an ANDA, the patent holder may consider this as an act of infringement, and can file suit for patent infringement.
3. If the patent holder sues the generic manufacturer within 45 days of the receipt of the notice letter, the FDA may not grant final approval of the generic application for 30 months from the time of loss of regulatory exclusivity, unless a district court rules for the generic drug manufacturer before then, allowing time for the patent challenge to be decided in court.
4. If the patent ruling is in favor of the generic-drug manufacturer, the patent holder may appeal the loss of the generic manufacturer's challenge. In this case, the appeals process takes an average of roughly 14 months.<sup>10</sup> During the appeals process, the generic drug maker may consider launching the generic drug "at risk," meaning before litigation has been resolved. However, if the patent holder wins the appeal, the patent holder can seek monetary damages for the revenues lost. Therefore, launching at risk can carry significant financial implications, especially in the case of a generic for a blockbuster medication. In practical terms, between the initial hearing process and potential appeal process, the patent holder may achieve up to an additional 30 to 45 months of effective exclusivity, beyond the point of loss of regulatory exclusivity.

The generic manufacturer's objective in challenging an existing patent is to initiate the patent-infringement evaluation process to coincide with the FDA's review of the drug application. In the best-case scenario, the FDA's review will be completed around the same time as the patent infringement case is decided, allowing the drug to be marketed as soon as possible thereafter.

#### SIDEBAR: The Relative Strengths of Patents

Although patents may seem to be an impregnable barrier to early generic competition, this is not necessarily the case. Certain types of patents are stronger than others. "Patents are never a sure thing. There is no perfect patent, I imagine," said roundtable participant Kurt Karst. "Patents can be found to be invalid or unenforceable, or perhaps even not infringed by a generic drug manufacturer."

Part of the reason relates to an imperfect system of reviewing and approving patents. Often, litigation contesting the validity of a patent involves materials or source information that the patent office didn't possess at the time of the initial patent approval or that was not fully understood by the reviewers.

In that context, new composition-of-matter patents seem to offer the strongest protection; they are the most difficult for generic drug manufacturers to challenge in court, according to the patent experts on the roundtable.

In contrast, method-of-use and formulation patents, which can include new routes of administration and unique drug delivery devices, may offer less protection. The reason for this vulnerability is that generic manufacturers can often utilize other mechanisms for drug delivery or develop new ways to bind molecules for oral or intravenous use.

Likewise, method-of-manufacturing patents may also offer less protection than a composition-of-matter patent. For example, drug makers may produce a bioequivalent product by manufacturing with different excipients or with other established methods.

#### Extending the Product Life Cycle and Protecting Product Revenue

As indicated earlier, the patent life remaining on a product at time of approval may be only 7 to 10 years. The complexities of mar-

ket exclusivity and patent litigation frustrate payers, physicians, patient groups, and other stakeholders. As there is no certainty as to the timing of availability of generics, these stakeholders cannot formulate a plan for the introduction of a generic version of a specific product. For example, uncertainty around patent expiration and generic product introduction makes pharmacy benefit planning (budgeting/formulary) more difficult.

### **SIDEBAR: Payer Perspective on Brand Extension**

Payers are frustrated by the extension of branded product life cycles through the granting of patents on isomers, metabolites, prodrugs, new delivery methods, and fixed-dose combinations; some of these modifications may improve aspects of drug effectiveness, safety, or adherence, while others may not.

Extending the life cycle of a brand is extremely profitable to the manufacturer of a product nearing the end of its patent life. "With a blockbuster drug, there's a lot to be gained by even a bit of an extension of that brand," said Peggy Johnson, RPh. If a branded drug's revenue averages \$1 billion per year, it has paid off the bulk of the research and development costs, and marketing and sales overhead years ago, to the point that perhaps 90% of its revenue in its final years of exclusivity is profit. This profit may be used to fund future research and development. Margins of this magnitude not only compel the efforts made to extend the life cycle as long as possible, but also greatly increases the amount a generic manufacturer who launches at risk, before patent litigation is complete, may have to compensate the branded manufacturer.

Another way manufacturers can extend revenues from their brand is to produce its own generic version of the drug; it markets its generic version as an "authorized generic." The FDA lists 980 authorized generics (although these include multiple dosages and forms of individual drugs), from Accupril (quinapril hydrochloride) to Zyvox (linezolid).<sup>11</sup>

### **Improving and Expanding a Drug's Utility**

Manufacturers often conduct additional research in an effort to enhance their marketed agents. Product enhancements may improve the drug's utility in clinical care, extend patent protection, and increase revenues. The result of the research may be

new uses and new indications. Many times, drug companies evaluate new routes of administration for their product (injectable, sublingual, intranasal, etc), which may increase absorption or enhance adherence.<sup>4</sup> For certain drugs, like asthma inhalers or insulin pens, this may be in the form of "improved" delivery devices customized for that drug.<sup>12</sup>

Commonly, manufacturers file patents on new drug formulations (eg, extended-release versions) or formulations that contain different excipients (to help stabilize the active ingredient, for instance). Furthermore, manufacturers may patent a new manufacturing process, which helps create greater quantities of medication more efficiently or with fewer inactive ingredients. As previously discussed, these improvements may not effectively shield the product from patent challenges.

The combination of the existing product with a new or other marketed agent is another way to extend the life cycle of a drug. This is the case with several diabetes agents (eg, combinations with metformin).

### **SIDEBAR: Price Increases on Products Nearing Patent Expiration**

Price increases toward the end of patent life are also a mechanism for maintaining revenue.<sup>13</sup> Payers object, as these increases have little to do with value of the product; rather, the increases are attempts to maximize revenue just before patent expiration. Dr Dunn said, "Historically, we have seen significant price increases in the 6 to 12 to 18 months leading up to a patent loss. There's nothing we can do about that. We're probably not going to take a drug off formulary and reinstate it 6 months later. But that's why we push so hard for price protection."

Ms Johnson added that price increases often go beyond the patent expiration to maximize revenue for the branded manufacturer. She stated, "Price protection rebates have been negotiated in part to address this scenario," not only for the originator product, but for other brands in the class. A new generic entering a drug category threatens "not just the drug that's going to lose its patent. Every brand name drug in that class feels their market share will be threatened because the class is going to be disrupted. So other drug makers in the class may raise their prices as well," Ms Johnson explained.

This leads, according to the payers, to the perception that the branded pharmaceutical companies will charge “pretty much whatever the market will bear,” and to the skepticism of payers that many actions taken by pharmaceutical companies to improve existing products are more product-line extensions than actual product enhancements.

### Payers and the Transition From Branded to Generic

Health plans, insurers, and PBMs monitor the anticipated patent expiration dates for high-cost agents, but as indicated earlier, their confidence level of exactly when a generic will be introduced is fairly low. Any anticipated price increases within 6 to 18 months prior to patent loss are discussed during pharmacy budget planning and P&T committee meetings.

#### **SIDEBAR: Payer Perspective on Planning for the Introduction of Generics**

Ms Johnson emphasized that “plans have become pretty good at what we call managing the pipeline of generic opportunity.”

The pharmacy executives noted that payers often start considering the potential effects of generics to these blockbusters 18 to 24 months ahead of time, especially if the P&T committee reviews a class once annually.

Although payers don’t actively manage their business around patents, *per se*, this can definitely be part of the planning process for blockbuster brands (eg, Lipitor [atorvastatin calcium], Prilosec [omeprazole], Nexium [esomeprazole], Crestor [rosuvastatin calcium], Abilify [aripiprazole]).

Dr Dunn agreed, adding that “Payers spend a good deal of time with actuaries and underwriters, trying to anticipate rebate and revenue changes, particularly for drugs in high-cost or high-utilization categories. We take a long-term approach to this. We’re probably not going to move drugs back and forth in anticipation of a patent loss.”

The near-term entry of a generic drug can also have implications for other medications in the same class. This can open negotiations for expiring contracts on

branded agents. Payers seek to determine which of several products in a therapeutic class may be first to go off-patent. This consideration may influence future plans, as can the first generic launch within a therapeutic class, which could have implications in P&T committee discussions—beyond the innovator product to other similar drugs. For example, if the category comprises therapeutically equivalent products, these other products may be subject to a step through the new generic.

In some cases, an impending generic entry into a drug class will have a very different impact, according to Dr Dunn: “If we do know a major brand is going off-patent in 6 months, for example, and another branded drug is entering the category, we’re much less likely to add that new brand drug to the formulary, because we don’t want to take market share away from the brand that’s going off-patent.” This tactic would enable the payer to save more money on a larger segment of the total patient population, by promoting the conversion of a higher volume of prescriptions within a class to the new generic medication by limiting competition from a “new and improved” brand entity.

#### **SIDEBAR: Formulary Placement of Recently Approved Generics**

Many P&T committees do address financial and budgeting questions, particularly in discussions of cost-effectiveness or value-based benefits. In most cases, an initial generic drug introduction does not usually require a P&T committee meeting for formulary inclusion. Discussions by the P&T committee involve comparative efficacy, safety, and then cost. Since the FDA has approved the agent, presumably as bioequivalent to the original brand, the first 2 issues are moot. Few or no head-to-head studies exist between “improved” brands and new generics to inform the value discussion, so payers often resort to cost discussions in these cases. In most cases, the new generic is offered at a significant discount to the branded product.

Ms Johnson remarked that when a generic is approved, generally, the new generic is automatically placed on the formulary (tier 1), and the innovator brand is usually

moved to nonpreferred status or excluded from the formulary (the latter in the case of a 2-tier or closed formulary). “It doesn’t generally impact tier positioning for the rest of the category, because we’ve already put a lot of time into crafting that strategy around cost-effectiveness and value.” However, she pointed out, other brands in the category may now be subject to step therapy with the new generic entity. Later, when more than one generic product becomes available in a class, a tipping point may be reached such that all brand products are relegated to nonpreferred or nonformulary status.

In certain situations, if the generic is not priced at a significant discount, it may be placed in a higher tier, solely based on cost (nonpreferred generic tier or a tier developed for brand name products). Tier designations may be related more to underlying drug cost rather than brand/generic classification.

## Case Studies

*During the second part of the roundtable, the moderator asked participants to comment on several case studies involving specific products, to gain feedback and perspective from the payers and attorneys regarding the particular circumstances surrounding the introduction of generic versions.*

### Case Study 1: Gleevec (imatinib)

Gleevec (imatinib) is indicated for the treatment of chronic myelogenous leukemia (CML). Novartis’ composition-of-matter patent for Gleevec expired in January 2016, and the first generic version of imatinib was marketed in the United States in February 2016 by Sun Pharmaceuticals.<sup>14</sup>

#### **SIDEBAR: Payer Perspectives on the Introduction of Generic Imatinib**

The introduction of a generic version of imatinib was followed closely by payer pharmacy directors, said Dr Dunn. “It is really a precedent setter for what we do in the oral oncology space. However, we didn’t change anything in anticipation of its launch, because the brand was not disadvantaged. We are now covering the generic and not covering the brand. It will shape anything that occurs in the future with this class of tyrosine-kinase inhibitors.”

“A patent litigation challenge added uncertainty to the timeline and ultimately delayed the generic launch for 7 months,” added Ms Johnson. “Novartis initiated discussions about extending brand contracting in light of an authorized generic launch and also offered patient copay discounts in order to compete with the generic product.”

Dr Dunn’s organization placed the generic on formulary immediately “because it didn’t affect contracts. It is on a specialty tier rather than the traditional generic tier, however. The brand was removed from formulary at the next P&T committee meeting. Today, other tyrosine-kinase inhibitor brands are stepped through the generic for the labeled indications via the prior authorization process.”

The short-term budget impact of this generic may be less than pharmacy directors anticipated, Dr Dunn pointed out, because the generic is not priced substantially less than the brand. However, its budget impact may grow over time, particularly with the expiration of the 180-day exclusivity period and the influx of additional generic competition. In addition, the ability to step other tyrosine-kinase inhibitors for CML through the generic for new patients should generate further cost savings.

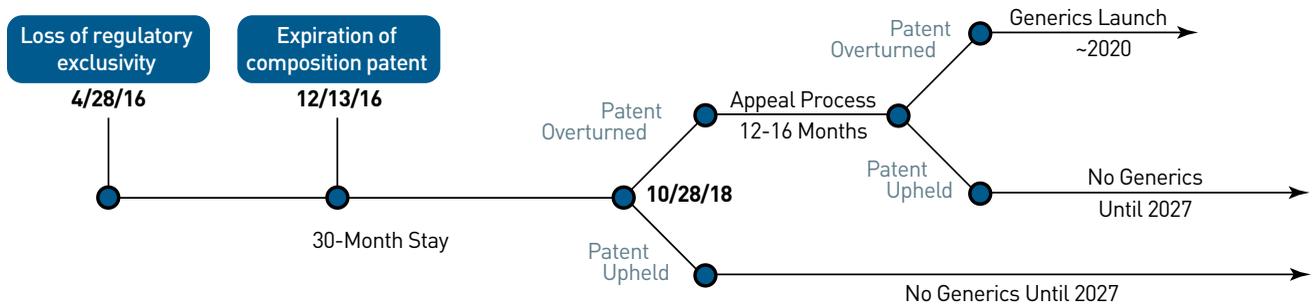
### Case Study 2: Zytiga (abiraterone acetate)

The FDA approved Zytiga (abiraterone acetate) for use in combination with prednisone for the treatment of men with metastatic castration-resistant prostate cancer who have received prior chemotherapy in April 2011.<sup>15</sup> A supplemental indication for use in men prior to receiving chemotherapy followed in December 2012.<sup>16</sup>

Three years after the initial approval of branded Zytiga (abiraterone acetate), the manufacturer of Zytiga received approval for an additional patent, which will extend the period of exclusivity beyond that of the composition-of-matter patent. This new intellectual property protection was a “method-of-use” patent, which covered the coadministration of prednisone (given as a separate pill) with Zytiga, a dosing regimen that was already prescribed in the FDA-approved product label. This patent was listed in the *Orange Book* and provides patent protection for Zytiga potentially well into 2027—more than 10 years beyond the expiration of the Zytiga molecule patent in late 2016.

The **Figure** shows the timeline of activity leading to the potential launch of a generic for Zytiga. The original 5 years of FDA regulatory exclusivity for Zytiga as a new chemical entity expired on April 28, 2016, and the composition-of-matter patent will expire on December

**FIGURE.** Zytiga Exclusivity Decision Tree



13, 2016. The 30-month stay on FDA approval for any generic expires in late October 2018, and should the manufacturer lose the patent case being subject to litigation brought by generic manufacturers to challenge the new dosing patent and choose to appeal the ruling, the appeals process may last a further 12 to 16 months, until the end of 2019. This would mean that the earliest a generic might reach the market is early 2020. Should the manufacturer win the dosing patent challenge by the generic manufacturers (or lose the challenge, but go on to win the appeal), the addition of the new dosing patent would extend patent protection for Zytiga into 2027.

**SIDEBAR: Panelist Perspectives on Zytiga Patent Protection**

According to W. Chad Shear, “Arguably, the additional patents offer an additional exclusivity for 20 years from their date of filing. However, those patents are subject to challenge by would-be generics, and are in fact being challenged right now in District Court and at the USPTO.”

The additional patent for Zytiga (patent 8,822,438) is listed in the FDA’s *Orange Book*. “Companies filing applications to market generic Zytiga will be required to certify to FDA that they do not infringe the dosing regimen patent,” added Kurt Karst. “This recently issued dosing regimen patent listing is therefore a barrier to generic competition, unless a court ultimately denies the patent as invalid and/or noninfringed.”

Health plans and formulary managers, though generally unaware of patent extension efforts or patent litigation status, do monitor the timing of potential generic availability of key products, as it is relatively easy to

track the expiry of regulatory exclusivity of branded products on the FDA website, and ANDA applications by generic companies trigger patent litigation, on which information is publicly available.

Ms Johnson stated, “I personally was not aware of the patent extension and potential for a dosing regimen patent related to the coadministration of prednisone. This is a fairly crowded category, so value [outcomes] will be a consideration relative to formulary placement.” She continued, “Contracts are generally not long term (more than 1-2 years) and generally have clauses related to market changes/new market entrants. Brand competition is a factor here, as well as patent extension.”

**Case Study 3: Namenda (memantine hydrochloride)/ Namenda XR (memantine hydrochloride, extended release)**

A “product hop” is the substitution—not addition—of a new branded formulation of a prescription drug for an old version by a manufacturer, with the intention of forestalling generic competition. Multiple examples of product hops have been seen over the years. For this case study, the focus was on an extended-release, once-daily dosage form of memantine (called Namenda XR), which was introduced by Forest Laboratories (now Allergan).<sup>17</sup> The manufacturer soon attempted to take away patient access to the immediate-release product, which was dosed twice daily.<sup>18</sup>

Furthermore, in a product hop example, the original formulation’s clinical effect is unaltered, but the medication is now somewhat different. In other words, the new version will not be considered AB-rated for substitution purposes. The sole beneficiary is the drug maker, who may avoid generic substitution and may reinforce its revenue stream.<sup>19</sup>

**SIDEBAR: Payer Perspectives on the “Product Hop”**

Unless there are clear benefits, payers are wary of the introduction of extended-release versions. “Generally, I would say these are not clinical issues. The perception is not very good from a payer perspective,” remarked Dr Dunn, “unless there are very explicit adherence issues [with the original drug] that will lead to obvious benefits [with the extended-release version]. We would treat any of these agents like a new brand. We don’t generally jump on board with these sustained-release or extended-release agents.”

Product hops tend to elicit more visceral reactions from payers, because they are associated with higher costs, with no additional clinical benefits. Ms Johnson noted that “the manufacturer’s attempt to take the immediate-release version off the market after introducing the XR version ‘didn’t work’. These product hops are not viewed as clinical differentiators or value drivers. We treat the extended-release products like other brands, and it’s much less likely they’re going to be positioned as preferred agents.”

Ms Johnson also emphasized that removal of the previous version prevented the validation of the new product’s value compared with the original product, making it more difficult to determine appropriate formulary positioning for the new product.

“This is really an egregious use of the patent extension, and it created a payer backlash,” commented Ms Johnson, because Forest sent the message that “it either doesn’t have faith in the original product, or that it simply wanted to move all of the Namenda business to the more expensive brand.”

The Namenda versus Namenda XR product hop landed in the court system, as the State of New York brought suit against Actavis (which purchased Forest, before being acquired itself by Allergan). A decision on May 22, 2015 by the US Court of Appeals for the Second Circuit agreed with a lower court ruling, stating that the “Defendants’ hard switch would likely have anticompetitive and exclusionary effects on competition in the memantine market, creating a ‘dangerous probability’ that Defendants would maintain their monopoly power after generics enter the market.”<sup>20</sup>

**Conclusion**

Pathways for the protection of pharmaceutical intellectual property are complex. The Hatch-Waxman Act of 1984 defined the pathway for generic drug approvals but also set patent and market exclusivities for different drug marketing scenarios. These protection pathways have evolved since that time, influenced by changes in legislation and the regulatory environment.

The Act’s system for patent protection and generic drug approval offers opportunities to not only guard intellectual property, but also to encourage innovation, including improvements to the drug in question. However, not all new pharmaceutical patents result in true innovation or in improvement in patient care, and payers are often skeptical of claims made around such product refinements.

Managed care stakeholders should have an understanding of pharmaceutical patents and ways in which intellectual property can be leveraged or extended, as this information can help clarify the availability of therapeutic alternatives, such as generics and the timing of their launches. With regard to blockbuster brands going off-patent, understanding this information can assist payers in budget planning, contract negotiation, and even P&T committee decision making.

An understanding of the patent system can also help improve payers’ appreciation of new product launches—for example, whether an approved product is a new molecular entity or simply a new formulation. This information can affect formulary positioning as well as patient care.

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**REFERENCES**

1. Song CH, Han JW. Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry. *Springerplus*. 2016;5(1):692-706. doi: 10.1186/s40064-016-2323-1.
2. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ*. 2016;47:20-33. doi: 10.1016/j.jhealeco.2016.01.012.
3. Potter A. Interpreting the BPCIA—is the “patent dance” mandatory? *The Columbia Science and*

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*Technology Law Review* website. <http://str.org/2015/03/31/interpreting-the-bpcia-is-the-patent-dance-mandatory>. Published March 31, 2015. Accessed August 16, 2016.

4. Gupta H, Kumar S, Roy SK, Gaud RS. Patent protection strategies. *J Pharm Bioallied Sci*. 2010;2(1):2-7. doi: 10.4103/0975-7406.62694.
5. U.S. Department Of Health And Human Services. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*. 36th ed. Silver Spring, MD: U.S. Food and Drug Administration; 2016. [www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/ucm071436.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/ucm071436.pdf). Accessed April 27, 2016.
6. Fernandez DS, Huie JT. Strategic balancing of patent and FDA approval processes to maximize market exclusivity. IP Loft website. [www.iploft.com/PTO-FDA.pdf](http://www.iploft.com/PTO-FDA.pdf). Accessed April 28, 2016.
7. Pensabene LB, Gregory D. Hatch-Waxman Act: overview. *Practical Law* website. <http://us.practicallaw.com/9-523-2397>. Accessed August 16, 2016.
8. Pharmaceutical Research and Manufacturers of America. 2016 PhRMA Annual Membership Survey. Pharmaceutical Research and Manufacturers of America website. [www.phrma.org/sites/default/files/pdf/annual-membership-survey-results.pdf](http://www.phrma.org/sites/default/files/pdf/annual-membership-survey-results.pdf). Published 2016. Accessed September 27, 2016.
9. Troy DE. Drug Price Competition and Patent Restoration Act of 1984 (Hatch-Waxman amendments). FDA website. [www.fda.gov/newsevents/testimony/ucm115033.htm](http://www.fda.gov/newsevents/testimony/ucm115033.htm). Published August 1, 2003. Accessed April 28, 2016.
10. Hungar TG, Sitzman M. Federal circuit year in review 2013/2014: intellectual property and appellate practice groups. Gibson, Dunn & Crutcher LLP website. [www.gibsondunn.com/publications/Documents/Federal-Circuit-2013-2014-Year-in-Review.pdf](http://www.gibsondunn.com/publications/Documents/Federal-Circuit-2013-2014-Year-in-Review.pdf). Published 2015. Accessed September 8, 2016.
11. FDA listing of authorized generics as of June 29, 2016. FDA website. [www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM183605.pdf](http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM183605.pdf). Accessed August 12, 2016.
12. Beall RF, Nickerson JW, Kaplan WA, Attaran A. Is patent "evergreening" restricting access to medicine/device combination products? *PLoS One*. 2016;11(2):e0148939. doi: 10.1371/journal.pone.0148939.
13. Staton T. 10 Big brands keep pumping out big bucks, with a little help from price hikes. *FiercePharma* website. [www.fiercepharma.com/sales-and-marketing/10-big-brands-keep-pumping-out-big-bucks-a-little-help-from-price-hikes](http://www.fiercepharma.com/sales-and-marketing/10-big-brands-keep-pumping-out-big-bucks-a-little-help-from-price-hikes). Published May 7, 2014. Accessed August 16, 2016.
14. Conti RM, Padula WV, Larson RA. Changing the cost of care for chronic myeloid leukemia: the availability of generic imatinib in the USA and the EU. *Ann Hematol*. 2015;94(suppl 2):S249-S257. doi: 10.1007/s00277-015-2319-x.
15. BTG plc: ZYTIGA™ (abiraterone acetate) approved in the US [press release]. London, UK: BTG International Ltd; May 3, 2011. [www.btgplc.com/media/press-releases/btg-plc-zytiga-abiraterone-acetate-approved-in-the-us/](http://www.btgplc.com/media/press-releases/btg-plc-zytiga-abiraterone-acetate-approved-in-the-us/). Accessed September 14, 2016.
16. NDA 202379/S-005 supplement approval (Zytiga). FDA website. [www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2012/202379Orig1s005ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2012/202379Orig1s005ltr.pdf). Accessed September 27, 2016.
17. Drug approval package: Namenda XR (memantine hydrochloride) 7 mg, 14 mg, 21 mg, & 28 mg extended release capsules. FDA website. [www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022525s000\\_namenda\\_xr\\_toc.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525s000_namenda_xr_toc.cfm). Published June 21, 2010. Accessed August 20, 2016.
18. Klusty T. A legal test for the pharmacy company practice of "product hopping." *AMA J Ethics*. 2015;17(8):760-762. doi: 10.1001/journalofethics.2015.17.8.hlw2-1508.
19. Lukens JT. Pharmaceutical product hop antitrust case reaches third circuit. Faruqi & Faruqi, LLP website. [www.faruqilaw.net/blog/id/174/pharmaceutical-product-hop-antitrust-case-reaches-third-circuit](http://www.faruqilaw.net/blog/id/174/pharmaceutical-product-hop-antitrust-case-reaches-third-circuit). Published June 2, 2016. Accessed August 20, 2016.
20. In the United States Court of Appeals for the Second Circuit: State of New York v. Actavis. Opinion No. 14-4624. Filed under seal May 22, 2015. ■

