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Generics Behaving Badly: Carve Outs, Off-Label Uses

Law360, New York (May 04, 2009) -- Patents have long been the crown jewels of the pharma industry. They protect pioneer therapies from generic competition and underwrite the enormous investment required for new drug research and development.

However, with an estimated $65 billion of drugs coming off patent protection in the next five years, generics stand ready to cash in on this bonanza. As the competitive landscape undergoes enormous changes, pioneers need to coordinate their IP and regulatory strategies to protect new investments in old drugs.

Hatch-Waxman: Then and Now

For the past 20 years, what made drug patents so valuable was the Orange Book (OB) patent listing scheme established by the Hatch-Waxman Act and the automatic injunctive effect that these patents had on generics.

Hatch-Waxman also ensured that a pioneer who researched and developed secondary drug features or new conditions of use would have sufficient time to recoup its investment before generics would be allowed to compete.

In most cases, the pioneer was protected either by getting three years of labeling exclusivity for new uses or conditions and/or by getting patent protection for any discoveries capable of being patented.

A generic would still be allowed to compete for uses and conditions not protected by exclusivity or patent, provided it could show the U.S. Food and Drug Administration that its drug was as safe and effective as the pioneer for all nonprotected conditions of use.

In theory, such partial competition by generics, often referred to as "skinny labeling," would lower the drug costs for some patients while still protecting the pioneer's investment, for a

limited time, in new conditions and discoveries.

The Skinny on Carve Outs

What the Hatch-Waxman framers could not have foreseen when they adopted the skinny labeling, or generic "carve out" rule, was the practice — rare 20 years ago but increasingly common today — of doctors prescribing drugs and pharmacists filling prescriptions for so-called off label uses.

Although a drug may not lawfully be marketed for an "off label" use, nothing prevents doctors from prescribing such use. Indeed, many drugs on the market (pioneer and generic) derive a significant share of their revenues from the treatments or uses that have never been approved by the FDA.

Compounding the problem for pioneers is the AB rating that a "carved out" generic can obtain which permits pharmacists — and in some states actually requires them — to substitute the generic for the pioneer even if prescribed "off label."

The competitive landscape continued to shift in favor of generics when, in 2003, the FDA overhauled its OB listing procedures, effectively making OB listing of patents a less powerful and versatile tool against generic competition.

Over the next five years, pioneers saw the drug competition pendulum swing decidedly in favor of the generic industry. Today, generic drugs account for over 60 percent of prescriptions written and over 20 percent of total drug sales.

Developing New Uses for Old Drugs

Pioneers have responded by developing new protectable uses for their drugs, including novel features or secondary conditions that appear on drug labels in the form of patent-protected language.

The effect on generic manufacturers is twofold: if the generic copies the pioneer label as generally required by the FDA rules, it risks infringing, or inducing infringement of, the pioneer patents; but if the generic seeks FDA permission to "carve out" the patent-protected language to avoid infringement, it limits its market to the nonprotected conditions or uses, which may only represent a small or declining share of the pioneer's market.

Yet pioneers remain concerned that the "carve out" rule, coupled with the practice of

prescribing and substituting generic drugs "off label," threatens their ability to recover the large investments needed to discover new uses or to improve the safety or efficacy profiles for old drugs. Recent FDA decisions on "carve out" cases indicate that the situation for pioneers is getting worse.

Since 2002, there have been nine FDA cases involving "skinny labeling," and only once has the FDA sided with the pioneer. These cases provide insight into how the FDA views the "carve out" issue.

When evaluating a generic "carve out" request, the test applied by the FDA is whether any of the patent-protected language is needed to make the generic as safe and effective as the pioneer for any of the conditions of use that are on the generic's label.

Thus, the "carve out" exception has been allowed by the FDA where a generic might be prescribed for an "off label" use, even if such use is the first line therapy for the pioneer drug; and where a new dosing regimen or harmful side effects are discovered for a patient population not previously targeted on the pioneer label; but not where safety or efficacy information is directed to "on label" patient populations unless such information already exists elsewhere on the pioneer label.

FDA "Carve Out" Implications for Pioneers

When looking at new investments in old drugs, pioneers should evaluate whether a proposed clinical study could lead to new uses that are protectable from future generic "carve outs." From the FDA cases, this would mean:

- If the new condition of use (i.e., the protected labeling language) involves a new indication that is not "intertwined" with other indications on the nonprotected conditions of use (NPCU) label, generic "carve outs" will generally be allowed.

- If the new use involves dosing, administration, warnings, etc., for a new patient population (i.e., one not on the NPCU label), generic "carve outs" will generally be allowed.

- If the new condition of use relates to safety or efficacy for an existing (NPCU label) patient population, generic "carve outs" will generally not be allowed.

- If the new condition of use relates to safety or efficacy for a new patient population that an existing (NPCU label) patient population is likely to become, generic "carve outs" will generally not be allowed.

New Patent Protection Strategies for Pioneers

Pioneers need to address all stages of their drug development life cycles — from claims drafting to clinical study design to labeling negotiations — to ensure they will recover their investments by way of the exclusivities and patent protections they seek.

Patent Claims Drafting

Discoveries made during pre-clinical and clinical investigations often lead to patentable features that appear on drug labels. Protected labeling language that comes from patents not listed in the OB cannot be "carved out" by generics and can present formidable barriers to generic entry. Examples include methods of manufacturing, diagnostic screening and distribution or tracking patents.

Patentable discoveries impacting safety or efficacy and drafted as method claims can appear on labels in the form of dosage/administration data, warnings, precautions, contraindications or adverse dug reactions. These types of patents must be listed in the OB and, theoretically, are eligible for "carve out."

How they appear on drug labels, however, will largely determine whether they can be omitted by generic drug manufacturers. As the "carve out" cases illustrate, patent claims that deal with safety and efficacy issues involving nonprotected indications or patient populations are more likely to survive "carve out" attempts than those that do not.

An aggressive patent prosecution strategy focused on life cycle protection should involve not only the careful "mining" of clinical data but also a closer working relationship with regulatory personnel involved with clinical study design.

By coordinating these two critical functions, while keeping an eye on the label, pioneers will be better positioned to ensure that their drug protections are maximized and clinical investments protected.

Clinical Study Design

The "carve out" cases teach some important lessons for clinical designers looking to protect drugs coming off exclusivity or patent protection, or who are simply looking to regain a competitive edge over generic competition.

Studies that are fashioned to add new indications will have a much greater chance of yielding

protected labeling language that cannot be "carved out" if the indications are intertwined with existing treatments.

Labeling omissions can also be thwarted if clinical studies are designed to add safety and efficacy information that address existing conditions of use or patient populations already targeted on the pioneer label.

Studies that focus on new conditions of use for patient sub-populations are also more likely to generate labeling that cannot be "carved out" if the sub-populations are sufficiently large in comparison to the drug's intended population, or if other sub-populations are likely to migrate into or out of the protected population.

None of this is to suggest that clinical studies can be easily altered or designed to ensure that, if successful, they will necessarily lead to labeling protections immune to generic "carve out."

However, study developers who understand how the FDA labeling rules operate, who can anticipate how labeling protections tie in with the clinical studies, and who are able to integrate their patent and regulatory functions to bring these protections about, stand the best chance of recovering their research and development costs ahead of generic entry.

FDA Labeling Negotiations

Nothing is more troubling to a pioneer than discovering its hard-earned patent claims do not correspond with the labeling approved for the drug.

This occurred in a recent litigation when a pioneer discovered that a miscommunication between its patent and regulatory departments resulted in the range of a key ingredient appearing on the drug label differently than claimed in the patent.

This mix-up gave generics an opening to label their drug within the range on the pioneer label with no risk of infringement. Had the patent and regulatory departments been better coordinated, generic entry would have had to await patent expiration.

For protected language to be of any value it must appear correctly on the pioneer label. This means that the pioneer's regulatory department needs to coordinate draft labeling language with their patent counterparts and possibly include them in negotiations with FDA staff during application review.

Individuals charged with labeling responsibilities should have superior negotiating skills, a firm understanding of how pioneer labels can be changed (e.g., to add protected language) without requiring FDA approval, and a sense of how to ensure that generics on the market adhere to their own labeling responsibilities.

OB Use Codes

Patents not listed in the OB cannot be "carved out" of a generic label. While this might look like an opportunity for pioneers to thwart generic entry by not listing eligible patents in the OB, they would be advised to approach such temptations with caution.

Under FDA rules, patent declarations, including a declaration that no patent can be listed, must be filed under "penalty of perjury" with the initial NDA, each supplemental filing, and upon NDA approval. A false declaration not only could land a pioneer in trouble with the FDA, but it might also raise an estoppel defense in subsequent infringement litigation.

OB use code listings, however, appear to be more flexible. Every method of use patent listed in the OB is assigned a use code, selected by the pioneer, which briefly describes the use claimed in the patent.

Use codes are important because a generic that seeks to "carve out" a patented condition use from the pioneer label must "carve out" all uses which fit the description.

For example, a listed patent that claims a specific combination drug use that is given a broad use code (e.g., "for use in combination with other drugs") could force generics to "carve out" all combination therapies on the pioneer label regardless of whether all are protected.

Conclusion

The competitive landscape continues to change dramatically for pioneer drug companies. Pioneers focused on protecting their investments in new uses for old drugs, or improvements to the safety or efficacy profile for these drugs, need to coordinate their patent and regulatory functions to maximize available protections.

Addressing patent protection during every stage of the drug development life cycle will ensure continued success in the marketplace.

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