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Drug Labeling Games – Skinny Labels Getting an FDA Assist

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Hatch-Waxman turns 30 this year. One measure of its success has been the phenomenal growth and universal acceptance of generic drugs, which now account for over 80% of all prescriptions filled in the U.S. While much of the industry's success was designed to come at the expense of pioneer drug developers, some clearly was unintended. One example how Hatch-Waxman has unexpectedly titled the balance in favor of generics is the evolution of FDA policies toward method of use patents.

Because of the way Hatch-Waxman has been implemented, many drug use patents have become unenforceable and thus, effectively worthless. Not only does this rob patent owners of their intellectual property rights, but also undermines a core tenet of the 1984 legislation which was to spur the development of new drug therapies. Now, the FDA may be getting ready to deal another blow to brand drugs that depend on use patents for market protection.

The Hatch-Waxman Balance

Hatch-Waxman was a grand bargain struck on behalf of the public health. It "promised" pioneer drug companies that if they invested in developing new drug therapies they would receive limited marketing exclusivity and a fair opportunity to assert their patents prior to any generic approval for those therapies. In return, generics were "promised" that if they agreed not to market their drugs for new therapies protected by pioneer patents, they would be allowed to enter the market for non-patented brand uses. Simply put, pioneers were given the clear expectation they would be able to recover their investments in new therapies even though generics might be on the market for the other approved uses.

To implement this intricate balance, the FDA adopted rules that required generic labels to be scrubbed of all information that would infringe the pioneer patent. Without safe and effective labeling for the patent protected use, "skinny labeled" generics could not lawfully be marketed in competition with the brand for that use. Unfortunately, the FDA had some other rules on its books that served to undermine the Hatch-Waxman balance. Instead of distinguishing between fully labeled and skinny labeled generics, the FDA adopted a therapeutic equivalence (TE) rating scheme that treated both types of generics equally.

Pharmacies, benefits managers and insurance companies had no way of knowing from the FDA's TE rating scheme which generics were safely and effectively labeled for all brand uses and which were not. And, because federal law and the pharmacy laws in most states rely on the FDA's TE rating for making drug substitutions, it meant that skinny labeled generics would be routinely substituted for brand prescriptions regardless of the intended use or risk to the patient (e.g. where safety information related to the patented use is absent from the label). The Hatch-Waxman framers could not have imagined a more incongruous outcome – pioneer use patents rendered worthless, research on new therapies disincentivized and patient safety put at risk.

Patent Use Codes

In an effort to address the growing problem of skinny labeled generic substitutions, some brands began manipulating the patent "use codes" submitted to the FDA for listing in the Orange Book next to the brand patent. The purpose of the use code is to instruct the FDA on the exact

language that must be removed from the brand label so the generic drug will not infringe the patented use. A use code that describes all uses on the brand label would prevent any skinny labeled generic from being approved because no authorized use for the drug would remain. Thus, a use code drafted more broadly than the patent claims could serve as a weapon to stop the skinny labeling of drugs protected only by use patents.

This practice was the focus of the Supreme Court decision in Caraco v. Novo Nordisk, 132 S.Ct. 1670 (2012) which involved a patented drug combination and a use code that went beyond the patent. The Supreme Court ruled in that case that a use code cannot be used to preclude generic marketing of a non-infringing use of the brand drug and ordered to use code to be narrowed ("a use code may [not] sweep more broadly than the patent"). The Court seemed oblivious to the false proposition that its holding clearly implied – that a narrowly drafted use code will preclude the infringing use of the brand drug by skinny labeled generics.

More recently, the FDA has been struggling with what to do about patent use codes that are narrower than the approved indication on the label. Under FDA policies cited with approval by the Court in Caraco, a narrow use code that overlaps a broad indication can only be carved out by omitting the entire indication. Therefore, the FDA is investigating whether an approved indication can be sub-divided into inherently authorized sub-indications to match the use code submitted by the brand so that generics may carve it out of their labels.

The drug at issue is Precedex, a sedation drug marketed by Hospira. The problem for generic applicants is that a narrow use code listed for the Orange Book patent forces the carve out of a broad indication on the label. Accordingly, they are seeking FDA permission to sub-divide the broad indication into sub-indications and then carve out the sub-indication covered by the use code. To do this, however, certain language would have to be added to the brand label and the FDA is unsure whether this would be permitted under the FD&C Act which generally requires brand and generic labels to use identical language. But a larger concern is what this policy might mean to brand drugs protected mainly (or solely) by narrow use patents. If the FDA allows a "re-labeling" of Precedex to facilitate skinny labeling by generics, it creates a precedent for the examination of other drugs also protected by narrow use codes, with ominous implications for brand manufacturers.

It's important to note that there is one slight wrinkle in the Precedex case that involves the generic exclusivity rights. Sandoz asserts that it has generic exclusivity and this will be lost if the drug label is revised because other ANDAs will be able to rescind their Paragraph IV certifications and file carve out requests that avoid the patent. Whether the loss of exclusivity is enough to force the FDA to back down on the re-labeling gambit remains to be seen.

A Push for Skinnier Labels

The FDA may be reading Caraco expansively to say that it is contrary to public policy for patent use codes to preclude generic marketing of non-infringing uses of the brand, even when such uses are only inherently authorized on the label. In theory, the FDA would be acting within its statutory authority to determine what uses (and sub-uses) are approved for a brand and how they should appear on the label. In reality, however, the FDA will be inviting generics to a challenge patent use codes to narrow them as much as possible per Caraco, and then seek a re-labeling of the brand to permit the narrow use codes to be carve out of skinny labeled generics. Below is an example of how this use code two-step might work.

An Orange Book listed patent claims a method of using Drug X to treat Condition Y in patients prior to surgery. The FDA approves Drug X to treat Condition Y in surgical patients. A patent use code is listed for Drug X that says "treatment of Condition Y in surgical patients," exactly matching the approved label indication. A skinny label carve out of this use is not possible because it would leave no indication on the generic label. However, in a Par IV litigation, the generic could argue that the use code is too broad and should be narrowed to cover only pre-surgical patients. If Court orders the use code to be narrowed, a generic could then approach the FDA to ask for the

approved indication to be divided into pre-surgical and post-surgical sub-indications. Skinny labeled generics could now carve out the pre-surgical use code and seek approval for post-surgical use only. These generics would then be able to go to market with a TE rating that allows them to be fully substituted for the brand for all uses, including pre-surgical.

What this presages for brands, is a future where only broad method of use patents will be of any value because only broad use codes will not be at risk of being narrowed – or having the brand's approved indications narrowed – to facilitate carve outs by skinny labeled generic drugs.