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**DRUG APPROVALS****21st Century Cures****21st Century Cures Act: No Cure for an FDA Patent Bias**

BY TERRY G. MAHN

One of the more controversial provisions in the legislative behemoth known as the 21<sup>st</sup> Century Cures Act, signed into law by President Obama on December 13, 2016, involves an overhaul of the regulatory approval process for new uses for old drugs, a fertile target for private investment in the important field of precision medicine. To incentivize investment in drugs that have already gone (or soon will go) generic, the Act makes it cheaper and easier for brand manufacturers to negotiate the FDA approval process. Instead of requiring multiple randomized well-controlled clinical trials, the current gold standard for all drug approvals, FDA will be allowed to rely on data from “observational studies, registries, and therapeutic use” to approve new indications for already-approved drugs. In addition, the

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legislation streamlines and expedites the review process for precision medicines and “qualified indications,” defined by the Act as cancer and other therapeutic uses “to be determined” by FDA.

Critics point out that this is Congress, once again, meddling in science; that a forced speeding up of FDA regulatory reviews will artificially short cut an approval process that has served the public for more than half a century; and in the end will lead to compromises in patient safety. But the real question is why these legislative incentives are needed in the first place. Here, some of the blame can be squarely placed on FDA. For years, FDA has promoted policies that discourage investment in new uses for drugs already on the market specifically, albeit unintentionally, undercutting its own efforts to spur advances in precision medicine. These policies target method of use patents and stem from an historic misreading of the Hatch-Waxman Act and FDA’s kowtowing to political pressure to help reduce public health care costs even if it means undermining the patent system on which much of the U.S. pharmaceutical business is based.

**Source of FDA’s Patent Bias**

Studies have shown that, on average, it costs \$2.6 billion and takes 14 years to bring a new drug product to market. During the time the drug compound is protected by patent, the brand manufacturer enjoys a mo-

nopoly. New uses discovered during this period are protected by the compound patent as well as any patents that may be issued for the new methods of use. Method patents, for example, might be obtained for new therapies or to improve drug safety and efficacy and might be based on new dosing regimens, combination uses or companion diagnostics used to identify specific patient genotypes as is the case of many precision medicines. But getting such new uses on the brand label can still be very expensive. While not as significant as obtaining the initial drug approval, investments in new uses can still run into the tens or hundreds of millions of dollars needed to fund R&D and the randomized clinical trials required for FDA approval.

If the brand manufacturer believes its investment can be safely returned, the company will have all the incentive it needs to develop new uses and precision medicines. If, however, generics are allowed to “free ride” on those investments the brand’s capital will go elsewhere. New uses would then become the responsibility of government agencies and non-profits, which have limited resources and few of the market-driven incentives for their efficient allocation. This is where patent protection becomes critical.

Congress recognized the problem when it enacted Hatch-Waxman in 1984. For drug compounds no longer protected by patent, Congress wanted to make sure that generic entry would not be slowed down or precluded by new patented indications added to the brand label. It did this by permitting generic manufacturers to “carve out” such indications and receive approval for only the non-protected uses. This would allow copycat generic drugs to be “skinny labeled” for the non-protected indications and marketed in parallel with the brand, which would be labeled for the patented indications. In theory, the public would benefit from early entry of low cost generic drugs and brands would still be incentivized to invest in new patented uses that would appear only on the brand label. In reality, it has never worked this way.

The problem centers on FDA’s policy of granting an AB “therapeutic equivalence” rating for generic drugs including skinny labeled generics. This all-important rating, listed in the FDA’s Orange Book, signifies that the generic is fully substitutable for the brand. Under the public health laws in many states, pharmacies are required to fill brand prescriptions with AB rated generics unless instructed otherwise by the prescribing physician. In most other states, pharmacies are merely required to request patient permission to substitute the generic – requests that are rarely refused due to the lower copy requirements imposed by most insurance companies. The upshot is that AB rated generic drugs are automatically substituted for the brand regardless of what the brand was prescribed for or how it was intended to be used. In the case of a skinny labeled generic, it means a “free ride” on the brand prescription even for the patented indications for which it was explicitly not approved. It is no wonder, therefore, that brands have shied away from investing in new therapies and precision medicines that cannot be protected by patent.

Whether the 21<sup>st</sup> Century Cures Act will alter current investment trajectories remains to be seen. If well-controlled clinical studies are no longer essential for approval and FDA reviews can be expedited, the Act may well stimulate private investment in “new cures” and precision medicine. However, that raises an even

thornier issue involving patient safety. If critics of the Act are truly concerned about patient safety being compromised by a watered down FDA review process, they should be doubly concerned that the current process allows safety information to be deliberately removed from generic labels when method of use patents are being avoided.

### **FDA’s Patent Policy on Carve Outs Undermines Patient Safety**

Under FDA rules, the only basis for refusing a use patent carve out is if the generic label would render the drug less safe or effective than the brand for any of the non-protected indications remaining on the label. Brands have challenged patent carve outs on numerous occasions, but FDA has yet to find a skinny label to be less safe or effective, even when the carved out omits critical safety information. This is because FDA’s carve out calculus requires that it “pretend” the generic drug will only be marketed for the non-protected uses on the label, even though it will knowingly bestow an AB rating to ensure the generic is fully substitutable for the patented use. Applying this twisted logic, FDA has approved generic drugs with entire clinical studies, replete with safety and efficacy data on the protected use, removed from the label. In one notable case, FDA approved a generic label redacted in 50 locations to omit any reference to the patented indication, despite the fact that the overwhelming majority of all prescriptions were being written for that indication. As the primary protector of our nation’s health, FDA appears dangerously unfazed that dozens of skinny labeled generics are knowingly administered to scores of patients with labeling that is demonstrably unsafe for the prescribed use.

What is even more troubling is the fact that FDA has the tools to prevent such risk taking yet it chooses not to use them. The FDA’s Orange Book, which is the authority for every generic’s coveted AB rating, states in Section 1.7 that: “There may be labeling differences among pharmaceutically equivalent products that require attention on the part of the health professional. The Agency may use notes in this publication to point out special situations such as potential differences between two drug products that have been evaluated as bioequivalent and otherwise therapeutically equivalent, when they should be brought to the attention of health professionals. These notes are contained in Section 1.8.”

Section 1.8 has never contained a single note that calls attention to a patent carve out. FDA also has the general authority to require skinny labeled generics to include a disclaimer or patient notice that calls attention to potentially unsafe drug substitutions, yet it has chosen not to exercise that authority. The end result is that these generic drugs get to ride free on brand patents while patient safety is being put at risk.

### **FDA’s New Rules Promote the Bias Against Method Patents**

In a recently concluded rulemaking to implement the 2003 Medicare Modernization Act, FDA adopted new rules that make it even tougher for brands to enforce certain types of method patents (81 Fed. Reg. 69580, Oct. 6, 2016). The flip side is that it will be easier for generics to carve such use patents out of their labels.

Aside from the possible safety concerns, these new rules undercut a foundational right granted by Hatch-Waxman for brand manufacturers to litigate their patents prior to generic launch.

Under Hatch-Waxman, a brand is required to list with FDA all patents that claim the drug for which it is seeking approval and all method of use patents for which a claim of infringement could reasonably be asserted. A generic that seeks FDA approval before such patents have expired is required to file a Paragraph IV certification that starts a process that allows the brand to bring an infringement action prior to launch. If the generic does not seek approval for the indication or condition of use claimed in a listed method patent, it files a “section viii” statement with FDA.

To determine whether a generic is, in fact, not seeking approval for a patented use, FDA looks to the “use code” filed by the brand with the listed patent. If the language of the use code is completely removed from the generic label and FDA determines that the generic would be no less safe or effective than the brand for all remaining uses, the generic drug is approved. If the use code cannot be completely removed, for example, if it reads on the only approved indication for the drug, FDA will reject the generic’s section viii statement. In that case, a generic still seeking approval prior to patent expiration would be required to file a Paragraph IV certification. The brand would then have the opportunity to litigate the patent prior to launch.

In theory, the brand is at liberty to draft whatever use code (up to a maximum of 240 characters) it believes must be removed from its label to avoid infringement. To keep the brand honest, FDA rules require the use code to be filed under penalty of perjury; in addition, the FDCA contains a counterclaim provision that allows a generic to directly challenge an improper use code in an infringement suit. FDA’s role in all of this is purely ministerial; it makes no infringement determinations and removes use code language from the brand label by rote. However, to put brand manufacturers at risk for the use codes they list in the Orange Book, the rules require the brand to specifically identify the claims in the patent that read on the drug and where on the label such use code language can be found.

The new rules address a problem that has surfaced periodically and on which the U.S. Supreme Court has clearly spoken. It concerns overbroad use codes – i.e. where the use code language claims more than what the method of use patent actually covers. In *Caraco Pharmaceutical Labs. v. Novo Nordisk A/S*, 132 S.Ct. 1670 (2012), the Supreme Court ruled that the statutory counterclaim can be used to challenge an overbroad use code, thus clearing up any confusion as to whether generic manufacturers had a remedy for overbroad or improper use codes. The Court also characterized an overbroad code as one containing language that would prevent the marketing of a generic drug for an approved use that would not infringe the listed patent. However, not content with the tools at hand – brand declarations under oath and the generic statutory counterclaim – FDA decided to go one step further with its new rules by instructing brand manufacturers on what use codes may or may not say, regardless of whether the brand reasonably believes its patent will be infringed by specific language on its label. Put simply, this is FDA meddling with a brand’s infringement analysis on behalf of generic applicants.

Under the new rules, a method patent that does not cover an indication or condition of use *in its entirety* must be listed with a use code that recites only the specific patent claim. In other words, it does not matter if the patent would reasonably be infringed by a labeled indication or condition of use, the use code must be narrowed to the actual claim language. In practice, this means that if there is any element in a patent claim that does not make its way onto the approved label, the use code must recite this element. Generics then, can file a section viii statement instead of a patent certification, seeking to carve out the narrow use code on the misguided theory that if all elements are not literally on the label, the generic drug cannot infringe and, therefore, is not being marketed for the patented use. But this stands patent law on its head. Moreover, it puts FDA in the role of infringement gatekeeper, a function that FDA has long maintained to be outside its statutory authority.

### Case Law and FDA Contradictions

Courts have long held that a patent can be infringed by the sale or use of a drug even where the label does not recite all of the claim elements. FDA learned this lesson directly in *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010), where the agency approved a use code carve out for “once a day dosing” on the belief that if this language was literally removed from the label, a section viii statement was an appropriate vehicle for avoiding the method patent. The Federal Circuit, however, told FDA that it was mistaken and that language elsewhere on the label would inevitably lead some users of the drug to infringe the patent. In *Bone Care Int’l, L.L.C. v. Roxane Labs., Inc.*, No. 09-CV-285 GMS, 2012 BL 143175 (D. Del. June 11, 2012), a generic drug was found to inherently infringe in some patients because the labeling instruction to administer the drug for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease on dialysis would induce infringement of a patent claiming the administration of the drug for the treatment of end stage renal disease (ESRD) and SHPT “because patients with chronic kidney disease on dialysis suffer from ESRD and the majority of patients with ESRD also suffer from SHPT.” And in *Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, No. LA CV13-08567 JAK (JCGx), 2014 BL 484395, at 5 (C.D. Cal. May 12, 2014), a label containing the phrase “for the treatment of ED” was found to specifically intend the drug also to be taken “for the treatment of penile fibrosis” (patent claim language that did not appear on the label) because “symptoms suffered by many ED patients are caused by an underlying penile fibrosis condition [and thus] the label will inevitably lead some consumers to practice the claimed method.”

FDA cannot turn a blind eye to this case law by asserting that its rules merely follow the statutory language that requires the listing of patents that “claim” an approved method of using the drug. In FDA’s view, if the patent does not literally claim the approved use on the label the use code cannot claim it either. But this misreads the law. The listing statute specifies patents that claim “a method of using such drug” and “with respect to which a claim of infringement could reasonably be asserted.” Significantly, it does not require the method of use to be an “approved” use, hence the importance of the second clause, which must be read to have substantive meaning under canons of statutory



construction. Read this way, the listing statute is clear that a use patent need not literally claim an approved use provided it would be reasonable to assert it against one not licensed to use or sell the drug. And there could be no justifiable basis for holding the use code language to a different or higher standard than the patent itself, nor for allowing the question of reasonableness to be determined by anyone other than the brand manufacturer. Thus, as long as the brand believes it would be reasonable to assert the patent against a seller or user of the drug based on certain labeling language, that language must be allowed to appear in the use code.

Ironically, FDA dealt with this very issue 13 years ago when it changed its listing rules for patents that claim the drug itself. Unlike use patents, drug patents are required to “claim the drug for which the applicant submitted the application.” Here, the statute is clear – a drug substance patent must claim the substance described in the drug application in order to be listed. Nonetheless, to maintain a “consistent interpretation of the ‘sameness’ principle in the patent listing and ANDA approval contexts” FDA decided to permit the listing of patents claiming polymorphs of the approved drug substance provided they were shown to be bioequivalent.

So what we have with FDA’s new rules, is the anomalous situation whereby a drug patent can be listed in the Orange Book even though it does not claim the approved drug, but certain use codes cannot be listed even though they claim an infringing use.

### **Use Codes Protect Against All Infringers**

As the Federal Circuit explained in *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman* 109 F.3d 756 (Fed. Cir. 1997) nearly two decades ago, a patent confers a “right to exclude” but that right does not necessarily arise from explicit language, for example, on a drug label. Instead, that right may arise from the fact that, when administered, the drug is being used for a purpose claimed by the patent. And while it is clear that a patent which claims a labeled use will necessarily be infringed by a drug sold under that label, it is also the case that a patent does not necessarily have to claim a labeled use in order to be infringed. This raises an ancillary concern about who can be the target of the brand’s claimed infringement.

FDA’s new use code rule focuses solely on the label language, a necessary requirement to show an intent to induce infringement by the generic seller. But the ge-

neric manufacturer is not the only possible target under Hatch-Waxman. The listing statute speaks of method patents that could reasonably be asserted against someone not licensed who “engaged in the manufacture, use, or sale of the drug.” The generic manufacturer is the obvious seller of the drug but it will be the doctors and patients who will be the infringing users. Yet, brand manufacturers do not go around suing doctors and patients for obvious reasons, thus the Hatch-Waxman patent amendments provide an exclusive remedy for an “artificial” use infringement brought under 35 U.S.C. § 271(e)(2). If infringement can be shown under this section of the patent statute, § 271(e)(4)(A) provides that “the court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent. . .” (emphasis added). This specific remedy says nothing about the type of infringement (direct or indirect) or the party doing the infringing (user or seller), but simply states that a drug “involved in [an] infringement” cannot be approved prior to patent expiration. If an intent to induce infringement by the generic seller can be shown, § 271(e)(4)(B) provides for injunctive relief against the seller. By contrast, if it can be shown that doctors or patients will use the drug in an infringing manner the statute provides a different remedy which is for the ANDA effective date to be the date of patent expiration.

### **Conclusion**

Precision medicine is the new buzzword in health care. Drugs once sold to the masses are being re-deployed for targeted use based on patient genotype, with improved safety and efficacy profiles. But the research and development of such drugs and the screening technologies needed for their precision is proving to be costly. To induce manufacturers to make new investments in old drugs, or in new drugs targeted for smaller patient markets, requires a studied quantification of the risk involved. This means a better understanding of the regulatory costs and timing for approval and confidence in the patent system to protect the needed investment. The 21<sup>st</sup> Century Cures Act takes important steps to address the first of these, i.e. the regulatory process; but FDA policies on method of use patents and approvals of skinny labeled generics will serve to undercut these efforts. And FDA’s misguided new use codes rules only make matters worse.