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Personalized Medicine – Slowing Down for "Free Riders"

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For the longest time, researchers and scientists could not figure out why some women with breast cancer responded favorably to tamoxifen while others do not. Even though 70% of breast cancer patients shared the same pathology, a third of those women taking tamoxifen received no benefit from the drug. Then, in September 2012, a research team from the University of Manchester's Paterson Institute for Cancer Research announced that it found the answer. A rare protein was located (a "biomarker") in women who were resistant to tamoxifen that appeared to block the drug's cancer-fighting activity. Doctors now predict that a simple "screen" will soon be developed to identify women who express this biomarker and spare them not only the expense, but also the false-hope of taking a drug that does them little good.

This is the future of personalized medicine (PM). With enough information about a patient's genetic, proteomic and metabolomic "profile," doctors someday will ensure that the right drug is administered at the right time and in the right amount, to safely and effectively treat almost any disease or condition. Because PM promises to improve patient care while reducing costs, it is often called the Holy Grail of healthcare. Nonetheless, the promise of PM still has significant hurdles to overcome, one of which is the economic paradox confronting drug companies. Many manufacturers, despite having superior research skills and extensive patient data files that could be enlisted in PM efforts, are electing to watch PM developments from the sidelines. Simply put, it is not often in a drug manufacturer's interest to invest in PM, especially when such investment can lead to lower drug sales. In the case of tamoxifen, drug manufactures are well aware that as soon as a cost-effective protein screen is developed, a third of their patients may stop taking their drugs.

Brand Economics and Personalized Medicine

A 2003 World Health Organization study revealed that approximately 50% of patients suffering from chronic illnesses fail to take their medications as prescribed. There are manifold reasons for this failing, but one factor is the belief that many drugs simply do not work. Recent studies have shown, for example, that even when drugs are taken as prescribed, less than 60% of patients actually respond to them. Together, these findings suggest – through no fault of drug manufacturers – that only 30% of prescription drugs end up treating the disease or condition for which they are intended. Conversely, it means that as much as 70% of the prescription drugs sold to consumers might just as well be flushed down the drain for what little good they do.

In 2011, U.S. prescription drug sales totaled approximately $325 billion. Applying the 70% "wastage" factor to this total ominously suggests that drug manufacturers may have sold over $227 billion worth of drugs that did not effectively treat the disease or condition for which they were prescribed. This figure represents a staggering waste of healthcare spending and explains why PM, which can ensure that drugs are better targeted to where they will be most effective, is

so widely supported. The challenge for regulators is how to incentivize drug manufacturers, whose business models are predicated on selling drugs rather than treating diseases, to support PM programs that advance public healthcare.

Generic Free Riding

Most drugs are approved following multi-phase clinical studies of large cohorts of individuals whose genomic characteristics vary widely. Typically then, the results project general correlations as to drug safety and efficacy that do not take into account the heterogeneity of the diseases being studied or variability of patient responses. It is only after the drug has been on the market and studied for some period of time that researchers are able to glean information relevant to specific populations or about disease profiles that can be used to "fine-tune" the drug for PM applications. By then, however, generic competition begins to loom and patent protection of the new drug composition is nearing its end. At this stage, the brand manufacturer will only be interested in pursuing PM applications for the drug if the manufacturer can be assured that the drug will continue to be protected from competition long enough for the brand to recover its investment.

In the case of tamoxifen, which went generic in 2003, four manufacturers currently sell this drug in the U.S. Not surprisingly, none of these companies participated in the University of Manchester studies, most likely because it was not in their financial interests to do so. Fortunately for breast cancer patients, there are well-heeled organizations that do not depend on drug industry funding or research to pursue PM opportunities. For many other diseases and conditions, however, well-funded constituencies may be harder to come by and PM investments difficult to incentivize.

The problem, of course, is "free riding" which occurs when one competitor receives the economic benefit of another's investment. Because generic manufacturers make no investment in drug research or development, they get to free ride (and undersell) the brand which might have to recover hundreds of millions of dollars in PM investments before it can return a profit. For new drug discoveries, free riding is largely kept in check by a combination of marketing exclusivity, which prevents the FDA from approving a generic drug for a limited period of time, and patent protection, which prevents any company from making or selling a drug before patent expiry. These protections keep generic drugs off the market until the brand, in theory, has had sufficient opportunity to recover its new drug investment costs. However, in the case of old drugs, these protections do not work nearly as well because once a drug goes generic it is virtually impossible to prevent generics from being sold for the new uses even when they are patent protected. Generics thus get to "free ride" on brand investments in old drugs, which is where many PM developments are thought to have their greatest return.

Personalized Medicine and the Drug Approval Process

A slight change in the tamoxifen facts should help illustrate the "free rider" problem. Suppose it was the brand manufacturer that discovered the telltale protein and patented a method of correlating that biomarker with the treatment of breast cancer using tamoxifen. The brand would put this new use information on its label, file the new patent in the FDA's Orange Book and, in theory, obtain protection against generic use of the biomarker discovery until the patent expired. If generic tamoxifen were already on the market, the patent would have little protective effect because doctors would know to test for the biomarker according to the brand label, but patients would still receive the low cost generic under state and federal drug substitution policies. But what if generic tamoxifen were not on the market when the protein discovery was made? Surprisingly, the result would be the same. This is because of the way generic drugs are required to be substituted for brands, by pharmacies and health insurance carriers in every state. Under either scenario, thanks to a quirk in the Hatch-Waxman Act, the brand derives no return on its PM investment.

Under Hatch-Waxman, when a brand patent is listed in the FDA's Orange Book, a generic is

required to certify to the patent before its drug can be approved. The generic can await patent expiry for FDA approval or it can challenge the patent by filing a so-called Paragraph IV certification. If the brand brings suit within 45 days of receiving notice of the generic's Paragraph IV certification, the FDA is required to suspend processing of the generic application for 30 months (which can be shortened or lengthened by court order). However, if the listed patent claims a method of using the drug, the generic can forego certification by filing a "section viii" statement, which tells the FDA that it is "carving" the patented use out of its label and will not be marketing the drug for such use. And, as long as the carved out generic label is as safe and effective as the brand for all non-protected conditions of use, the FDA is required to approve the carve out. Moreover, a section viii approval for a generic goes into the Orange Book as A-rated and "therapeutically equivalent" to the brand. This means the generic with the carved out use is fully substitutable for the brand throughout the U.S.

Over the years, brand manufacturers have petitioned the FDA to prevent specific section viii carve outs, but have failed in 15 out of 16 attempts. Even when a brand raises valid safety or efficacy concerns, the FDA has shown a reluctance to hold up generic approvals. In the recent U.S. Supreme Court case involving the drug Prandin (repaglinide), brand-conducted studies found that 25% of diabetes patients experienced improved efficacy when taking the drug in combination with another drug as compared to taking it alone. The brand manufacturer patented the combination therapy, put it on the drug label and petitioned FDA not to approve any generic seeking to carve out the combination therapy because it would not be as effective as Prandin in treating diabetes. Nonetheless, and despite unchallenged evidence of improved efficacy in diabetes patients taking the combination therapy, the FDA denied the petition. Soon, generic repaglinide will be available for substitution of the brand for a combination therapy found nowhere on the generic label.

Arguably, this was the first PM carve out case to come before the FDA. Here, an "old drug" was studied and found to be more effective in treating its targeted disease in a segment of the population when taken as a combination therapy. The FDA's failure to apply its carve out rules in this case sent a discouraging message to brands that might otherwise be looking to invest in PM.

Conclusion

The economic incentive for brand manufacturers to invest in PM discoveries in drugs that are about to go generic is virtually non-existent. Once a brand goes generic it can lose up to 80% of its market share in the first few months and over 90% by the time a second generic enters the market. And as brands come to realize how easy it is for generics to "free ride" the system with section viii carve outs and full substitution for patented brand uses they may remain firmly planted on the PM sidelines.

It is important for the FDA to realize that the future of PM requires the active participation of drug manufacturers and that independent research organizations cannot go it alone. The easiest way to keep drug manufacturers in the PM game is to recognize that such discoveries fundamentally enhance the efficacy profile of older drugs. This means that the patented information describing such discoveries should be required on all drug labels and not carved out by free riders. For old drugs like tamoxifen that have gone generic, independent research organizations may be the only source for PM funding. But for newer drugs that have not yet entered the generic space, brand manufacturers need to be incentivized to make the financial commitments than can make these drugs more personal and thus, more effective for all patients. One of the best ways to do this is by recognizing the critical role that patents play in the PM discovery process and enforcing the labeling policies that are "on the books" that will prevent free riding by generics.

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