With the Food and Drug Administration (FDA) placing greater emphasis on Phase IV postmarket surveillance, ongoing public concern over adverse events leading to the removal from the market of a number of drugs in the last few years and the increasingly clamorous conversation over the equitable allocation and cost of healthcare, it’s not surprising that the focus and interest in personalized medicine continues to grow. The discovery, in the wake of the sequencing of the human genome in 2003, that many individuals react differently to the same drug due to discrete differences in the genetic code is now being used to match the right drug to the right person in the right dose.

A recent report in Science estimated current sales of pharmacogenomic therapies at a mere $3.65 billion, compared to total pharmaceutical sales of $550 billion. While it is true that sales of personalized medicines presently represent just a fraction of the total market of pharmaceuticals, it is an impressive fraction given that the “birth” of personalized medicine occurred only five years ago.

Today, there are approximately 14 targeted therapies already on the market and almost two dozen targeted therapies in late-stage clinical trials expected to reach the market within the next 10 years. While these “targeted therapies” continue to win conceptual support in the wider medical and patient communities, the products based on this development paradigm are expected to be part of mainstream medical practice within 10 years.

With the enormous amount of attention now being devoted to these theranostics – drugs dependent upon tests to provide prescribing or dosing information – and the implementation of personalized medicine strategies across the pharmaceutical industry, the need has arisen for the co-development and commercialization of companion diagnostic tests to identify...
relevant biomarkers. The pharmaceutical and diagnostic industries now need to work together in a collaborative environment more often and earlier in the development process than they ever have before. As the pharmaceutical industry continues to shift greater focus onto the development of targeted therapies, the individual drug teams tasked with the development of these targeted therapies face a host of business considerations they have never before encountered. With this increased focus on early stage co-development of biomarkers, and the potential post-launch dependency of these new therapies on the availability of a biomarker result, more thoughtful consideration must be given to the issue of the future ownership of any intellectual property (IP) created as a result of these early collaborations.

Co-development of early stage biomarkers that may ultimately be incorporated into commercialized companion diagnostics fundamentally alters the decisions that the clinical and drug teams must make about what, when and how — or even if — to protect potential biomarker IP in early phase development. While the pharmaceutical industry has historically not focused on retaining ownership of this type of IP, its future ownership will now become essential to the development process and to the ultimate success of these theranostics. Further, early stage biomarker IP, wisely managed, might be utilized as a potentially potent means of providing needed incentives to the diagnostic partner whose business model does not encompass the kind of pre-launch investment that is typical of the pharmaceutical industry and is so necessary for full adoption of these new therapies.

We have found that there are at least four ways in which the collaborative partners might leverage IP created in the process of early stage biomarker co-development. (This article is not intended to be a comprehensive analysis of the multitude of IP issues that the drug teams must take into account when making relevant business decisions relating to biomarker IP.)

While this article is by no means exhaustive, as the possibilities are really only limited by the creativity of the partners and what they each are willing to agree to, it does touch upon what might be considered the most obvious choices — which are perhaps not always the best choices — and discusses some innovative ways to consider sharing biomarker IP.

**Potential Scenarios**

What follows are the most viable and workable options for structuring collaborative agreements between a pharmaceutical and diagnostic partner for the purposes of co-development of a theranostic. For the pharmaceutical partner, the main consideration in structuring these agreements is freedom to operate, balanced against the time value of money. For the diagnostic partner, these agreements can be used to provide incentives to ensure they are fully engaged in the development process for the long haul of the drug development lifecycle. Further, some percentage of ownership in this early biomarker IP may provide the means for the diagnostic partner to potentially recoup their return on investment (ROI) should the drug falter in clinical trials or fail to gain FDA approval thereby giving them some greater security to enter into such co-development agreements.

**#1. Pharmaceutical Partner Owns All Biomarker IP**

While exclusive ownership by the pharmaceutical partner of all biomarker IP would initially appear to be the best and most obvious option, as it would allow the pharmaceutical partner to retain the greatest control over the biomarker, it has some substantial flaws. First, it may be very difficult to achieve in practice as many early phase biomarker discoveries occur with university and/or research organizations whose contracts often mandate at least some IP ownership.

Second, while this option would certainly provide the pharmaceutical partner with the greatest freedom to operate, especially where a different diagnostic partner is required to commercialize the test, it would likely require a substantial outlay of sums up-front to retain all of the IP. Even if the pharmaceutical partner chose this path, it is unlikely in this day and age that the diagnostic partner would accept this situation without requiring unacceptable excessive upfront payments.

However, even if a diagnostic partner were willing to accept such an arrangement, consideration should be given to the fact that it may be necessary for one diagnostic partner to be fully engaged in the entire lifecycle of the drug development process, regardless of the point at which the collaboration is initiated. While it is commonly believed that loyalty and focus may be had at the end of a large, lump sum payment, comments from a number of individuals within the diagnostic industry itself indicate that they are looking for more from this shift in the drug development paradigm than to simply continue to be thought of and treated as mere suppliers. It is therefore unlikely that a large upfront payment will achieve the goal of a successful, integrated, long-term collaboration between the pharmaceutical and diagnostic partners over the long lifecycle of drug development.

**#2. Pharmaceutical Partner Retains All Biomarker IP Ownership: Grant of Non-Exclusive Rights**

Another potential scenario would be
for the pharmaceutical partner to retain exclusive ownership of all biomarker IP but with non-exclusive rights granted back to the diagnostic collaborator. This option may require less of an upfront payment from the pharmaceutical partner than other options, although they would presumably have to provide some cash payment for retaining almost all of the IP rights. While this option may be the most economical in terms of present day, short term spending, it provides little protection in ensuring the pharmaceutical partner’s compound is first to market and retains a period of exclusivity. If no time restriction is incorporated into the agreement during which the diagnostic partner may not work the invention, then the diagnostic partner could foreseeably engage with a therapy competitor during the development lifecycle of the first drug and help a competitor bring a companion test based on the same biomarker to market for a similar or competing therapy before or at the same time as the pharmaceutical partner. Thus, incorporation of a time restriction should be a primary consideration to provide a greater measure of competitive protection. However, this option may do little to provide necessary incentives to the diagnostic partner to stay on the much longer drug development lifecycle path.

One way to potentially provide even greater protection in this scenario would be for the pharmaceutical partner to provide a greater upfront payment to maintain some period of linked collaboration tied to the approval process with a one time extension period in the event the FDA is slower than usual in approving the theranostic or comes back and requests more data. Serious consideration should be given, however, as to whether this is the message the pharmaceutical partner wants to send to its diagnostic partner: it does not truly engage the diagnostic partner in any way, either providing a true stake in the present development process or the possibility to recoup ROI elsewhere. This typically “pharma-centric” model may not be the wisest choice in this new paradigm of drug development where the pharmaceutical partner requires a test to enable use of their therapy. Both partners have to look at what works best for the idea of theranostic development overall and ensure that both partners can find a way to recoup investment and make a profit.

#3. Joint Biomarker IP Ownership
Yet another option would be for both partners to share joint ownership of the biomarker IP with both able to work or sub-license the invention. This is probably a better model overall in terms of keeping the diagnostic partner engaged and providing needed incentives. While this option is likely to require reduced cash incentives upfront it may necessitate some time limit so that if the drug fails, the diagnostic partner could go elsewhere with it or it could incorporate the option of a right of first refusal for the pharmaceutical partner. This would give the pharmaceutical partner some breathing room to consider whether they think the drug is likely to gain approval with more work and thus retain and possibly prevent the diagnostic partner from engaging a therapy competitor.

On the other hand, if the pharmaceutical partner really put both feet in, they could take this route, offset some of the development fees up-front for the diagnostic partner and try to work in some sort of royalty back to themselves if their drug fails and the diagnostic partner goes to a therapy competitor. This would remove the diagnostic partner’s burden upfront and provide the pharmaceutical partner with some, albeit very small, possibility of recouping some diagnostic development costs or act as a write-off against earnings. The royalty back from the diagnostic partner might only be of a symbolic nature at this early development stage, designed to indicate that the pharmaceutical partner is not actually developing both the drug and test for free, but is simply providing an early assist to the fully integrated diagnostic partner. The concept of “royalties” has already been floated by a number of diagnostic companies in terms of their receiving them from the pharmaceutical partners based on overall sales of theranostics in recognition of these new drugs dependency on the companion tests. It might behoove those truly forward thinking diagnostic companies who wish to ensure their long-term stake in this new drug development paradigm shift to consider the option of royalties flowing in the other direction, even only as a symbolic gesture, as an apt demonstration of their commitment to this process.
#4. Diagnostic Partner Retains All Biomarker IP Ownership: Grant of Non-Exclusive Rights

Another option would be for the pharmaceutical partner to actually grant full ownership in the biomarker IP to the diagnostic partner in exchange for grant of a limited right to the biomarker back to the pharmaceutical partner for its purposes only. This option not only potentially obviates the need for up-front payments to the diagnostic partner but clearly sends the message to the diagnostic partner that they are more than simply a service provider and are truly a stakeholder in the theranostic co-development process.

While there may be some perceived logic to this scenario within the pharmaceutical industry as, after all, they are “not a diagnostic company,” the pharmaceutical partner must be fully aware of the implications of choosing this route. This scenario is likely to result in the therapy uptake in a theranostic application being absolutely dependent on the full involvement and ongoing commitment of the diagnostic partner. Given the years between biomarker discovery and therapy commercialization, a high likelihood exists that the interests of the diagnostic partner would not be aligned with the interests of the therapy at launch absent a concerted and carefully coordinated partnership.

It might be possible to address these concerns, however, by including the option to negotiate either an exclusive or non-exclusive right to the biomarker IP for greater flexibility and to ensure the pharmaceutical partner has the space to incorporate a time limited, exclusive option. These additional points would appear to give the pharmaceutical partner the greatest room to operate while reducing upfront development costs or at least contemplate them on a much smaller scale. This also provides the greatest incentive to the diagnostic partner to really engage in the process while providing the pharmaceutical partner with some comfort that the diagnostic partner is not going to undercut their co-development efforts with a therapy competitor.

**Conclusion**

Regardless of the ultimate structure of agreements to co-develop theranostics, the prior discussion should make clear that early stage biomarker IP is a significant resource that, with proper consideration, can be made to work to both partners’ advantages. The prior scenarios also point to two trends in the pharmaceutical and diagnostic industries that we anticipate seeing develop as the discussion around early stage biomarker IP in the personalized medicine space continues to develop.

The first trend is the fact that the diagnostic industry has identified that diagnostic IP, when connected to a drug or drug class, has far greater value than stand-alone diagnostic IP. Historically, diagnostic IP was regarded by the pharmaceutical industry as circumventable under the premise that another option could be found as there is usually “more than one way to skin a cat.” Further, prior to the mid-1990s and continuing up until today, only a few companies (e.g., Roche and Unipath) have consistently invested in building and, more importantly, protecting diagnostic IP portfolios. However, with the increasing scientific link to disease pathways, risk assessments and direct drug responders, new competitive vigor has been injected into diagnostic IP and this, in turn, is attracting fresh investment capital into higher net worth molecular or DNA-based diagnostic companies (e.g., Myriad and Genzyme). This new investment in diagnostic IP allows diagnostic companies to be fresh entrants into the treatment marketplace. At present, the leading diagnostic companies have about a decade or more lead into the biomarker IP “supermarket” than, in general, that of the pharmaceutical industry.

The second trend is the fact that the pharmaceutical industry has not yet necessarily realized the full value and worth of protecting early stage biomarker IP. While IP connected with drug or treatment pathways has traditionally been associated with aggressive protection and in-licensing, the discovery or value creation surrounding biomarker IP as part of the discovery process has, to date, been largely disregarded or neglected. As recently as one to two years ago, few pharmaceutical companies even had “biomarker strategies.” Today, various presentations by a select few pharmaceutical companies (e.g., Roche, Novartis and Lilly) on the Personalized Medicine circuit indicate that this is changing. Although perhaps a little late to the biomarker IP “supermarket,” the antenna of some pharmaceutical IP departments is now clearly working.

These two trends would appear to augur well for the eventual mutual sharing of early stage biomarker IP in the pursuit of shared clinical goals. Indeed, this paper speaks directly to the mechanics of such sharing. To date, however, we have found that “collision” rather than “collaboration” is the most likely outcome of pharmaceutical and diagnostic industry interactions for the following two reasons:

First, true co-development and IP collaboration means a true partnership and is likely to mean royalties on biomarkers flowing to the pharmaceutical partner and royalties on drug sales flowing to the diagnostic partner. Based on the authors’ experience, one can see little willingness, dialogue or business creation enabling this scenario. Instead, entrenched views of “what is mine is mine and what is yours is yours” appear to be the predomi-
nant and hobbling attitude. In fact, the focus with regard to this possibility is so narrow that it is often simply the use of the word “royalty” on which people get stuck, and broadening that perspective is often as simple as changing that word or discussing the fungibility of funds. The authors foresee this attitude as unsustainable for theranostics where a drug’s success is likely to be more dependent upon the biomarker IP guiding its use than on the marketing muscle of the pharmaceutical company.

Second, a narrow focus on biomarker IP as the sole “freedom to operate” mechanism misses the technological point. The development and use of high quality testing platforms is still in flux and, at present, is owned by multiple companies in the diagnostic field, e.g., PCR, IHT, imaging demethylation, etc. However, these platforms are finite in terms of the number and quality of the answers they are providing to doctors and patients. In short, the future consolidation of the optimum diagnostic platforms for use in the personalized medicine market is a significant threat to pharmaceutical companies’ freedom to operate. Companies like Roche, Siemens and GE have already started consolidating these technologies and the pharmaceutical industry, with a few notable exceptions, appears once again to be late to the marketplace.

The authors believe that tomorrow’s IP map will continue to be imperfect but that these pockets of “freedom to operate” will continue to exist. At the same time, smart biomarker strategies, for example in oncology or neurology, combined with strategic acquisition of the best enabling technologies, will create significant minefields for the pharmaceutical industry to traverse. It is unlikely that such IP bundling will be used to prevent access since that would be unethical and not in the interests of societal welfare, but it is likely to lead to higher costs of entry for the pharmaceutical industry. It appears to the authors that the industry is simply not yet ready for that debate.

1. RF Service, Going From Genome to Pill, 308 SCI, 1858, 1858-1860 (2005).
3. Personalized Medicine, The Emerging Pharmacogenomics Revolution (Price Waterhouse Cooper, (Feb. 2005)).
4. Information contained in this article is provided in the context of guiding sound business decisions with an eye toward directing future negotiations with potential collaborative partners. Although these considerations may touch on areas of IP, contract and competition law, this information is not intended as legal advice and legal counsel should be consulted in each specific context to be certain that any such legal issues are addressed directly.

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