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Licensing challenges in complex markets

Why it pays to invest in strategic portfolio creation

Inside the new pharma patent dynamic

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How operating companies are using NPEs to make money and shape markets

Vertical disintegration in the pharma industry and the role of IP

New business models are emerging in the pharmaceutical industry, so the way in which companies and service providers in the sector handle IP issues is going to have to change

By Sherry Knowles and Matthew Higgins

Morgan Stanley announced this year that the pharmaceutical industry should replace all internal research and development (R&D) with search and development (S&D). Provocatively, it predicted that eliminating all basic research could provide a threefold increase in returns and triple the number of new approved drugs (“Pharmaceuticals: Exit Research and Create Value”, Andrew Baum, Morgan Stanley, January 2010).

Large pharmaceutical companies have already been pursuing a goal of at least partial externalisation, mostly through licensing, for some time. Significant dependence on external technology in Food and Drug Administration-approved products already exists (see Figure 1). For example, GlaxoSmithKline (GSK) has a publicly stated goal of achieving at least 50% externalisation of basic research. As part of this initiative, in 2009 it announced the termination of many of its research programmes in neurosciences (historic for the development of Paxil, Wellbutrin, Lamictal and Requip), to free up resources for investment in external R&D.

Medical Marketing and Media, quoting a study by Datamonitor, reports that GSK topped the list of licensing deals in 2009 with 67, followed by Pfizer (47), Sanofi-Aventis (41), AstraZeneca (38) and Merck (36). This is consistent with the overall trend over the past 15 years: Deloitte Recap reports that alliances by pharmaceutical firms grew

from 590 in 1995 to more than 1,590 in 2008 (see Figure 2). This trend does not appear to be letting up; for example, the chief executive of Roche told Bloomberg recently that the company executed 65 deals in 2009 and plans as many again in 2010 – and this is on top of its US\$3 billion investment to complete its purchase of Genentech.

These numbers illustrate that pharmaceutical companies are becoming more risk averse in the identification of drug leads and early development, preferring to license new leads than to try to find leads internally. Coupled with this licensing activity has been a dramatic increase in pharmaceutical corporate venture capital investment, through which companies are making small bets on a variety of early-stage firms and then deciding at a later date to license or acquire.

As indicated above, the licensing of drug inventions by pharma is not new. What is new, however, is the scale on which it is now happening or planned to fill depleted pipelines, reduce perceived risk and decrease costs. But will it work? This stark change in business model warrants a fresh review of risk factors to determine whether, on the whole, the industry will be better off and what role intellectual asset managers can play.

Vertical disintegration as a proposed vehicle for risk reduction

Vertical integration exists when all functions of the industrial value chain, from research to distribution and sale, occur at one company. Outsourcing pharmaceutical research, a form of vertical disintegration, is considered a way to share financial risk with a partner – typically, a venture-backed emerging company, university or mid-cap company with a licensable asset.

A typical example of a risk-sharing approach would be as follows. Large Pharma

Percentage of new drugs approved based on externally derived technology, 1989-2004, for those companies with 10 or more approved products in the US. For a drug to be designated “externally derived”, more than 50% of the associated patents identified in the FDA Orange Book had to have originated outside the firm. “N” represents the total number of NDAs identified in the FDA Orange Book over the time period and % is the percentage of those drugs that meet the above criteria.

Source: FDA Orange Book and Ceccagnoli, M, Graham, S, Higgins, M, Lee, J, 2010, “Productivity and the role of complementary assets in firm’s demand for technology innovation”, *Industrial and Corporate Change* 19(3), 839-869.

Figure 1.

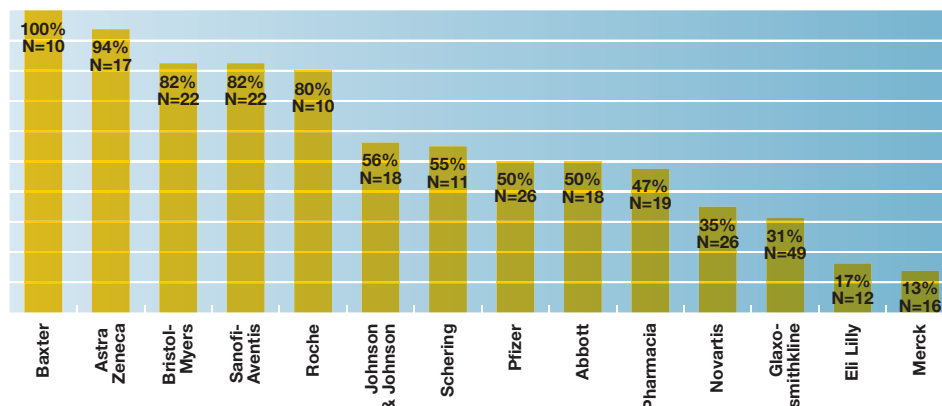
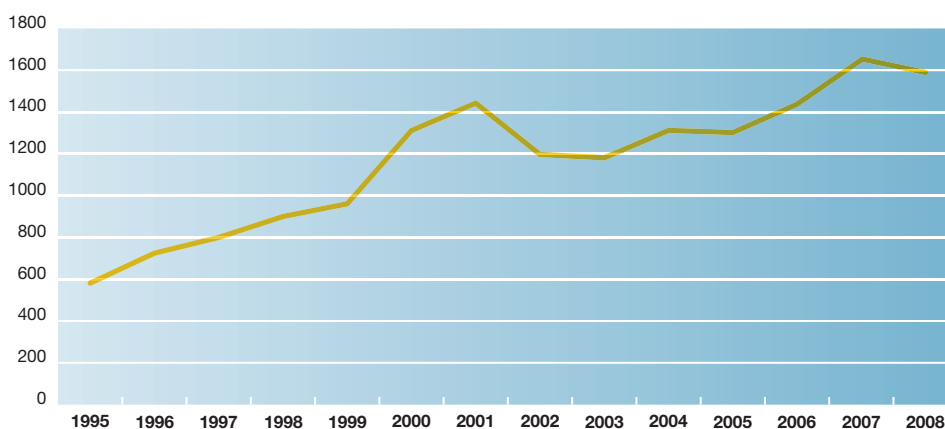


Figure 2.



Total number of alliances by pharmaceutical firms as reported by Deloitte Recap (www.recap.com) from January 1995 to December 2008. Data constructed and accessed by authors on 12th October 2010.

A takes an exclusive option on a promising new pre-clinical drug lead owned by Emerging Company B. A pays B fees (which can be in the form of an upfront payment and milestones, full-time equivalents or a running payment) which equal some part, but not all, of the research expenses for early-stage work, including human clinical trials. B has control of the research decisions up to proof of concept and maintains control of patent prosecution. At proof of concept – which is typically at the end of a Phase II clinical trial – A must decide whether to exercise the option and, if so, must make milestone and perhaps other payments. A may then take control of the clinical trials or may allow B to retain control through drug approval. A may or may not take over the patent responsibility at this stage, depending on the terms of the contract. If the drug fails at proof of concept, A has lost only a portion of what it cost and B has shared the risk. If the drug research is successful, A’s cost can be as low as 50% or less of the cost of research, and theoretically A can double the number of drugs it develops (at least

through early stage – the most risky time), while B gets the bonus of having more responsibility for its asset, as well as a share of the commercial return.

There are perceived cost savings and financial risk reductions in this model; however, there is also a counterbalanced increase in marketing and sales risks. Normally, pharma builds considerable downstream complementary assets that are often drug specific (eg, sales forces). This creates a lock-in effect for specific therapeutic categories, which has necessitated these companies going to the external technology markets when internal productivity failed. In a pure S&D model, 100% of the development risk is moved external to the company, which is left with under-deployed complementary assets when it is unable to find suitable matches. Vertical disintegration may thus also require some alteration to the traditional sales force structure.

Moreover, and critically, many studies have overlooked another key risk in the pharma vertical disintegration model: intellectual property.

A transformational IP paradigm

While vertical disintegration may decrease the R&D cost of failed drug leads, it creates a transformational IP paradigm for the company. If not managed properly, this can increase risks to the company and, as an industry trend, can actually lead to destabilisation over the longer term.

Potential IP risks include:

- Increased risk caused by allocation of control and inherent conflicts of interest in licensing arrangements.
- Increased risk of patent invalidation.
- Increased cost of assets caused by dramatic increase in number and intensity of licensees.
- Licensing of less than optimal assets (assets with warts), due to a more limited supply of external assets.

In the vertically integrated model, large pharma typically has in-house patent counsel who handle prosecution. A well-run in-house patent department has patent quality assurance programmes which emphasise best practices in drafting and prosecution. Presumably, the attorneys have been trained in potential pitfalls that could lead to invalidation, and are kept closely up to date on the company's own litigation experiences and those of like companies. Patent attorneys can easily review notebook pages and data which are discussed with the scientists and other attorneys. This fully transparent landscape is valuable to determine whether the final granted patent can be relied on by the company to hold a market – a critical assessment for accurate long-range forecasts.

In contrast, in the vertically disintegrated model, patent prosecution is typically the responsibility of a third-party company or institution which may or may not understand, or have had any experience with, Hatch-Waxman generic litigation or expected global litigation scenarios. Moreover, the licensor may have only a few research assets and no commercial experience. Layers may also be added if the licensor uses outside counsel who are junior-level attorneys or inexperienced in the field. During due diligence, counsel for the large pharma may not be allowed to inspect notebooks or raw data before giving a binding offer; or this potential evidence may simply not be requested. Sometimes access to inventors may even be restricted during the negotiation phase, or important contracts or documents withheld or heavily redacted.

Further complicating the dynamic, the large pharma licensee may disagree with the licensor on prosecution strategy. However,

the licensor usually retains prosecution control, while the licensee must defend the prosecution decisions during later litigation, which it typically controls. The licensor may also make short-term motivated decisions in prosecution to accomplish a quick patent grant (which it thinks will increase deal valuation or trigger a milestone), which can add to longer-term litigation risk – for example, not disclosing a reference that could be considered material because the licensor might get a final office action that it thinks could affect deal terms. Moreover, the licensor may also take an overly optimistic view of experimental data to defend the patentability of its asset to a potential or current licensee, and include that overly optimistic view in the file history. In other words, the licensee and the licensor may have a conflict of interest: one may think short term and the other long term, which is exacerbated by front-loaded payments.

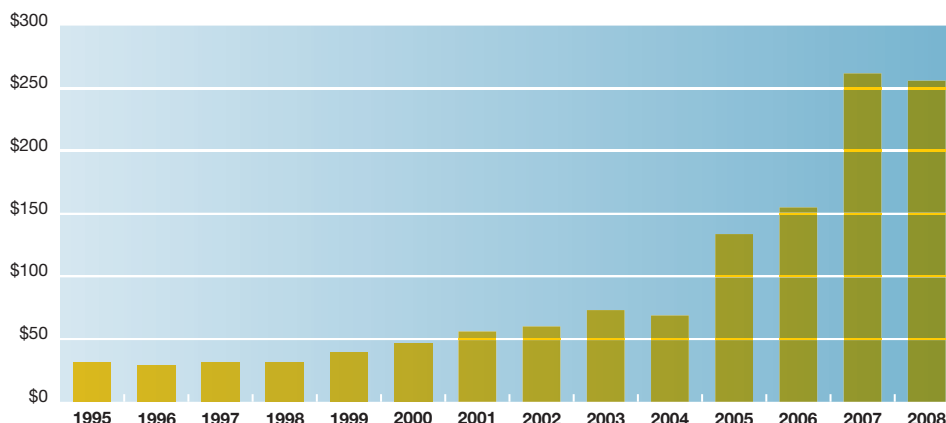
Increased risk

Here are some hypothetical examples of pharma licensing issues which highlight the complexity caused by control provisions and inherent conflicts of interest.

In a first example, Emerging Company B with promising lead drug DEF in a potential large market is in advanced discussions with three large pharmas for an in-licensing deal. B understands the potential value of the product and asks for US\$150 million as an upfront payment, even though the product is only in early Phase II trials. Two of the large pharmas seek comprehensive patent due diligence, including dates of conception of the drug, copies of notebook pages and all original comparative data with a third-party competitive drug. The third large pharma, anxious to do the deal, agrees to commit without some of this data and document review. B tells the other two pharmas that they will have to enter a bid without this information (because B is concerned it might get into an interference fight over priority and doesn't want to share invention documents). Senior management of all three large pharmas desperately want the deal and pressure the business development staff and patent attorneys to accept it without full due diligence.

In a second example, Emerging Company B with drug asset licensed to Large Pharma A is bought by A's competitor, Large Pharma C. If A is not protected with suitable termination and reversion rights, C can slow the progress of the project or decrease assets allocated to it, which can affect the viability of the drug's development.

Figure 3.



Average licence deal value (US\$ millions) as reported by Deloitte Recap (www.recap.com) from January 1995 to December 2008 for licences over US\$1m. Data constructed and accessed by authors on 12th October 2010.

In a third example, Emerging Company B has discovered two promising drug leads with similar chemical structures for related indications. To maximise value, the board of B decides to license them separately to two different companies. Large Pharma A and Large Pharma C each take exclusive licences to develop at high cost. However, the two drug leads were described in the same parent patent application. A conflict arises when A and C do not agree on patent strategy, so B has difficulty with prosecution. In Europe, the time for filing additional divisional applications has expired (under the new EU law that limits the timeframe in which divisionals can be filed), so A and C are required to protect their products with the same patents, which leads to further litigation complications. In the United States, B divides the application into two continuation applications. B allows A and C to control prosecution of the continuation application, but B stays materially involved with both. A cites art on the record in its continuation application that C does not think needs to be cited in its co-pending application. Further, A makes arguments in a response to an office action which are arguably inconsistent with arguments made by C in its separate application. These actions raise duty of disclosure issues and potential inequitable conduct because B remains involved with both and the cases are related. However, neither A nor C sufficiently agrees on strategy to allow for a combined approach.

In a fourth example, Large Pharma A licenses promising clinical trial drug DEF from Emerging Company B. Large Pharma C is granted a patent that DEF literally infringes. C also has a drug in late-stage clinical trials, GHI, that will directly compete with DEF. The patent licensed from B to A then issues with claims that

GHI will also infringe. B attempts to independently settle with C and receive a royalty on competing product GHI. A chooses not to settle with C and remains exposed to infringement risk with C when it sells DEF, and has to compete with C's product GHI. A sues B for settling with C, and C sues A for patent infringement.

In a final example, A enters into a collaboration with University B to develop future compounds identified as a result of B's discovery of a new enzyme and signalling pathway. B's Technology Transfer Office negotiates a licence with A to an initial patent application, but refuses to license later developed compounds, methods or pathways developed during the term of the collaboration, on the basis that the inventions do not exist yet so the university cannot assess their value. As each new invention is identified, the university seeks a separate licence agreement with separate financial terms. As A licenses the arising IP in the collaboration, the ultimate payments due start to stack up, decreasing the potential value of the commercialisation. If A does not license the arising IP, including new methods to use the compound being developed, or new pathway tools, it may be blocked from full commercialisation or follow-on indications.

Scenarios such as the above are not directly caused by vertical disintegration; however, such a shift can multiply the problems. Any company can absorb a few licensing problems, but when the industry shifts to a predominant S&D model, amplification of these problems can increase the overall systematic risk in the industry.

Increased risk of patent invalidation

Often under-appreciated is the fact that even where a new blockbuster is discovered, sails through the regulatory authorities and is approved on first pass, and where an efficient

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manufacturing process is in place, top-line insurance reimbursement is granted, an experienced and ready sales force exists and there is risk sharing in the process, if the patents cannot hold the market until repayment of expenses and an adequate return on investment is achieved, then the entire project is a net loss for the company.

In a recent study, Grabowski and Kyle (*Managerial and Decision Economics*, 2007) demonstrate that between 1995 and 2005, average market exclusivity periods declined by almost 20% to 11.2 years. Furthermore, they found an increasing number of drugs subject to early generic entry, including drugs with modest and average sales; and drugs with larger sales having increasing generic challenges. They concluded that Hatch-Waxman patent challenges have negatively affected market exclusivity over this period.

The number and scope of issues which have been litigated in the United States are a credit to the creativity (or frivolousness) of generic lawyers, and a minefield for the commercialising entity. Issues raised include inequitable conduct, inventorship, claim scope and interpretation, interpretation of data and notebooks, omitted data, inconsistent statements made in agency filings in the United States or other countries, improper certifications (including small entity status), disclosure of bias by declarants, documents filed with the Patent and Trademark Office outside deadlines and so on. Even a quick review of recent publication *Patent Claim Construction in the Federal Circuit* (Edward Manzo, Ed, 2010) will prompt pharma companies to reach for the Pepto Bismol.

In the vertical disintegration model, some patents will have been obtained by emerging companies with no pharma litigation experience. How this will play out remains to be seen, but given the complexity of litigation

issues, it should be a cause for concern. Further, as described above, exacerbating the lack of experience is the potential short-term mindset of inexperienced companies, which may end up taking prosecution risks to speed the acquisition of patents for financial triggers or deal advantages.

Increased cost of assets

As Morgan Stanley points out, licensing acts as an options risk reversal strategy: downside risk is lower than for an internally developed equivalent, but the upside benefits are also limited due to possible royalties and milestones. However, even this limited upside or blue-sky scenario assumes that the costs for these external products will not escalate as a function of the changing environment. If demand goes up due to a shift towards S&D and supply does not increase, resulting costs will increase (and even possibly surpass the equivalent internal costs) – a trend that we can already see occurring (see Figure 3).

Licensing in of less than optimal assets

Given a limited supply of licensable drug leads, large pharmas are more likely to consider assets with no patent rights and assets which are covered by patents with fully identified prosecution problems. Where the asset has no associated patent rights, there is a high risk that the pharma will only cover costs or, worse, lose money on the investment.

For a range of reasons, including validity concerns and because of antitrust risks associated with potential inequitable conduct assertions by generic companies in the United States, pharma may more frequently consider licensing drugs with impressive biological activity without any obligation to assert or defend patents. In this case, pharmas would value the asset based on

Action plan



As traditional business models in the pharmaceutical industry undergo fundamental changes, the onus is on IP asset managers to help to reduce risks:

- **Pharma industry-wide duty of care:** The industry should consistently demand comprehensive and deep IP due diligence before executing deals to decrease the possibility of unknown problems which change the risk profile post-deal. This will increase the quality of the deals done and minimise a licensor's position that "the other company didn't ask for that".
- **Business development negotiators:** Business teams should set the tone that IP structure and governance will be critical to the deal and establish meaningful joint IP committees to manage licensed IP. They should also resist price inflation as competition increases for drug assets (which makes it increasingly hard to break even). This will work only if it is practised as an industry (with each acting independently in a pro-competitive fashion).
- **Transaction attorneys:** Deal lawyers will need to be increasingly sensitive to the effect of control provisions and inherent conflicts of interest on behaviour, and work out issues well in advance. Joint IP steering committees which meet frequently are useful, with the commercialising entity holding the tie-breaker vote.
- **Licensee patent attorneys:** Licensee patent attorneys will need to learn to work closely and collaboratively with licensor patent attorneys who have control over prosecution to help to identify and minimise prosecution risks. Conflicts of interest should be promptly escalated to a joint IP steering committee.
- **Licensors:** Smart licensors will prepare for this changing paradigm by learning to think like large pharma – this will mean valuing long-term success over short-term wins, and understanding what large pharma wants to see (and not see) in a patent prosecution strategy. Select outside counsel who are experienced and have a track record in the types of asset being developed. Associating with an adviser with large pharma experience may minimise painful devaluation of the asset or, worse yet, inability to commercialise an asset.

the regulatory data exclusivity period only, with a compressed (or negative) return. This trend would harm society as a whole, because less money would be available for future new drugs, and new drugs have been correlated with increased quality of life and lifespan. It can also cause a conflict with the licensor, which might want to assert its patent and try for the upside (but has probably never experienced the pain of an invalidity or inequitable conduct decision and downstream ramifications).

Vital role for IP managers

As the pharmaceutical industry shifts to a vertically disintegrated model, it will have to raise the bar on the quality of deals done, and identify and be willing to say no to the wrong deals (and deal terms). This means substantially increasing the amount of information collected in pre-deal due diligence and structuring creative new forms of deal terms to avoid substantially increasing long-term risk. It may also mean changing the types of deal terms offered as a means to minimise conflicts of interest in

decision making which affect long-term protection of the asset (eg, clawbacks, change of control and step-downs in royalties or elimination of milestone payments as penalties for short-term rationales and other errors).

It will be up to intellectual asset managers – including corporate business development specialists and transactional attorneys, as well as patent attorneys – to change how they think and work, in order to manage risk adequately. Due to the very long time periods for R&D, commercialisation and then patent litigation, it will be a long time before we know the actual effect of vertical disintegration on the pharma industry. It is undeniable that IP asset managers will play a vital role in its success. **iam**

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