

## ***Recent evolution of the licensing agreements in the Biotechnology and key factors determining their successes and values***

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### *History*

During the last 30 years, more specifically since 1978 and in particular since the Eli Lilly acquisition of a recombinant insulin developed by Genentech, the licensing agreements (licensing) between the actors of the biotech and pharmaceutical industry became the rule. One could observe since the beginning of this initiatory exchange, a rise to power of the agreements binding the emerging biotech companies and the large pharmaceutical companies (known as “blue chips”). As an example, 117 agreements were observed in 1994 on the world market. Ten years later, 502 agreements were signed, so an increase of 329%<sup>1</sup>.

The paradigm describing these exchanges was until now the following: the biotechnological company discovers and develops the molecule at early stages (preclinical, phase I and II) and the pharmaceutical company, after buying those molecules, undertakes to finalize the development and to market the product through its own sales network. More recently, specialized companies brilliantly occupied a new commercial niche by buying molecules at the development stage just to resell them later with a significant added value (cf Debiopharm). In the same way, certain biotech companies (Serono, Amgen, etc) consolidated their position little by little in order to reach a sufficient level of maturity allowing them, either to develop and market their molecules, or just simply to acquire molecules from other developers (in-licensing). In addition, pharmaceutical companies do not hesitate to reproduce “biotech” models by creating spin-offs (Aventis: Proskelia became ProStrakan or Novoxel more recently) with financial interests (participation in the capital, shares) and the possibility of in-licensing products under development.

In parallel, a clear reversal in the balance of power between the biotech and pharma industries was observed<sup>2</sup>: the pharma companies were recently confronted with the massive emergence generic drugs (in France in 5 weeks, the generic took 50% of the market of Omeprazole) and with a certain deficiency in their pipeline of development. The biotech industry is at the head of the growth of the pharmaceutical market. Thus, in search of new promising molecules the pharmaceutical companies heavily invested in biotechnology. Wild competition between the pharma companies which made it possible for biotech companies to choose their trade partners more easily. Moreover, this situation also made it possible to keep rights during the development of the molecule (non-exclusive licence) and during the process of marketing (ex: Eyetech Pharmaceuticals sealed an agreement with Pfizer in December 2002 for the development and the common marketing of the molecule pegaptanib (Macugen)). A recent survey underlines this competitive pressure by showing that between 2000 and 2004, the number of agreements concerning “young” molecules strongly increased<sup>3</sup>. Their financial value also doubled to reach an average of 72 million \$ (10 agreements beyond of 100 million \$). Lastly, the agreements concerning the more advanced molecules (phase III) underwent a big increase of their initial payment (upfront) and royalties.

However, these licensing agreements between biotech and pharma, initially generators of value, can in the event of failure, have a dramatic impact on the biotech. In 2003, at the time of the announcement by AstraZeneca that the compound in-licensed from the NicOx company in phase II (AZD3582), had not met the necessary criteria to pass into phase III, the quotation of NicOx' shares was suspended. With the removal of suspension two days later, the NicOx share plummeted 83,67 %!

As we saw, the licensing agreements strongly evolved/moved. In this context, the factors playing a great part in the success and the development of an agreement are as follows: timing, the choice of partner and the evaluation of the value of a licence.

### *Timing*

At which stage do we have to buy or sell a molecule? When does one have to start the discussions?

The answer to these questions comprises at least a common point: the opposite relation between the risk and the total value of the licence (upfront, royalties and milestones). The level of risk is directly related to the stage of development of the molecule. The “younger” the molecule is the more risk there is of development being stopped due to unconvincing results. The level of risk is also influenced by the therapeutic indication the molecule is developed for: for example if the number of potential patients is high (cf. Alzheimer) one can of course expect higher incomes. In short, the decision determining the purchase of a molecule depends on the strategy of each company and its degree of risk aversion.

Lastly, the companies in search of a new trade must initiate discussions as early as possible<sup>2</sup>. As described above, the current market trend shows a great competition for the molecules in early stage. This competition has the advantage of making it possible for a biotech company to choose its partner for itself and to obtain a subjective indication of the value of its licence. As we will see it later, a value can be estimated objectively with means of simulations.

### *The choice of partner*

The licensing agreements in the biotechnological sector are very often characterized by a relatively long duration. This is explained by the desire of the actors to limit the financial risks (pharma) and to increase stability (biotech). This approach makes it possible for the pharmaceutical companies to be granted the rights on several molecules or only one and the derivatives which will be developed successively. Among the famous examples of trade agreements, Roche agreement with Genentech is frequently quoted. Since 1990, thanks to this alliance Roche obtained six of its best molecules (ex: Avastin, Herceptin, etc). On top of that, Genentech obtained a long-term financial stability. Another example relates to Pfizer's ten years agreement with Medarex during which approximately 50 therapeutic antibodies were produced. Lastly, Roche was recently granted nearly exclusive rights on a molecule candidate to the clinical phases (PSI-6130) developed by Pharmasset. In an interesting way, this agreement also relates to the pro-molecules derived from the PSI-6130.

At this stage, it becomes obvious that the choice of the partner is a crucial factor for the viability of associations between companies. But the philosophy of a pharma company is often different from that of a biotech company. Compromises must be found and the companies must especially share a long-term vision. Thus the biotech company will select the partner that suits its needs in the best possible way<sup>2</sup>. In case of doubts, a no protest clause of the licence can be added to the contract if future disagreements are foreseeable. In all events,

the reputation of a company as partner of choice can be seriously sullied if an agreement fails (example Astrazeneca & NicOx).

### *The evaluation*

The correct evaluation of a licence value is certainly a dominating factor to approach a negotiation. In this case, models exist making it possible to estimate their value? Is there a mean of selecting the most promising molecule? At the current hour, there are primarily three financial models which are used to determine the value of a licence: NPV (Net Present Value)<sup>4,5</sup>, decisional trees<sup>5</sup> and real options<sup>6,7</sup>.

The NPV is the method general practitioners most commonly use. The value of a license is determined by summing up the benefits and expenditures expected for the years to come and then each annual value is discounted backwards in order to obtain the value today (discounting). When the NPV is negative, the project is regarded as non profitable. On the contrary, a positive value indicates that the project is viable. This method assumes that the costs and benefits to come are certain, but does not take the factor of uncertainty which prevails in the biotech and pharma world into account (ex: therapeutic failures, modifications of the regulations, etc).

The two other methods (decisional trees, real options) take the factor of uncertainty into account in the form of probabilities defined for the success rate of each stage of the molecule development. In the same way, the probabilities of sales according to different scenario benchmarking can be introduced. Lastly, unlike the model of decisional tree, the real options also uses a cross relation at each stage expressing the expected increase or decrease of the asset value.

Nevertheless, just like the NPV, these two methods are limited by the ability of the user to precisely determine with precision the key parameters such as long term interest rates and inflation, the development costs, the benefits, etc, which are significantly influenced by intangible factors (psychology of the markets, appearance of candidates, etc).

Contrary to the methods described above which are based primarily on financial parameters (quantitative), recent progress in the data-processing field made it possible to formulate a method also taking qualitative aspects into account (indication, mechanisms of action, etc). This solution based on algorithms of datamining (literally “excavation of data”) aims at highlighting, the particular molecules within a group of molecules which have common characteristics by using the different parameters describing a molecule<sup>8</sup>:

- Scientific aspects: indications, action mechanisms, degree of innovation, etc
- Financial aspects: development costs, benefits, peaks of sales, etc
- Legal aspects: patent expiration time, etc

The result of the molecules comparison, where all parameters are simultaneously taken into account, visually outlines a competitive space where various groups of molecules having sufficiently important affinities are gathered. Thus, thanks to this innovating method, it becomes possible to:

- Compare a molecule under development for which one would like to evaluate its potential to reach the same development level as related more advanced molecules (“benchmarks”),
- Select whether the molecule is to be sold or bought (returned expected, costs, etc) when compared using chosen parameters,
- Determine the suitable timing for the sale or purchase of the molecule.

## Conclusion

As we saw previously, recent changes deeply affected the licensing agreements. This rise of biotech companies' power was not fortuitous. It rises from their high degree of innovation, their diversity and technology employed. In this context, the pharmaceutical companies were born from new entities, sometimes forcing their company philosophy upon the biotech companies and especially affecting their hegemony. Moreover, the arrival of "generics" (Teva, Sandoz, etc) contributed to accentuate the competition for the acquisition of molecules from biotech companies. This fratricidal conflict resulted in a value increase of early stage molecules and thus in an increase of financial risk. In this context, the use of the methods to evaluate new projects was spread little by little in the industry to estimate this risk. Today, the NPV is largely used supported by more complex methods (decisional trees, real options). This is undoubtedly more refined when considering the random aspect of the molecule development. Lastly, the accession of the datamining will undoubtedly bring more definite answers, by the integration of multiple parameters simultaneously.

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