On the stage division mechanism in pharmaceuticals development processes

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This paper contributes to the understanding of a recent trend taking place in the pharmaceutical industry, whereby large companies develop a meaningful number of alliances with smaller firms, to share stages of drug development processes. Small firms tend to operate in earlier stages and intuitively, this may suggest that this is because they are more efficient, or more willing, than larger firms to take such early risk. In exchange, larger firms would afford the higher development costs of later phases. In this article we argue that the intuition appears correct if large companies have enough resources to develop in-house all potentially interesting projects, but not necessarily so when they are resource constrained.

Introduction

Empirical evidence in the pharmaceutical industry [1–5] indicates how a significant percentage of large pharmaceutical firms' pipelines, is due to products in-licensed from other firms, frequently small innovative ones.

This often means that the various stages of a drug development process, going from the discovery of a pharmaceutical compound to its final commercialization, are conducted by different firms. Typically in such stage division small firms tend to operate in the early, often preclinical and less costly, stages of a drug development process while large companies tend to invest directly in the later, more costly, stages closer to the commercialization of the pharmaceutical compound. Indeed, while pre-human/preclinical phases account for about 27.2% of the overall R&D investments, clinical trials account for 47.8%, while the remaining 25% is spent for drug approval 6.1%, pharmacovigilance 12.9% and uncategorized expenditures 6.1% [6]. For this reason, stage division appears also to be a mechanism through which risk is exchanged against cost bearing, among firms of different size, since clearly compounds getting to more advanced phases have a higher likelihood of reaching commercialization.

Though division of labour in inventive activities is a well-known phenomenon [1,7,8,11], given the economic impact and significance of the pharmaceutical industry, understanding the specifics of such trend in drug development stage division is very important.

The literature [9–11] has, so far, been focused on explaining, mostly in terms of economies of scale and scope, why large firms differentiate their portfolio of compounds under development, as well as on the role of alliances between biotech and large firms and the strategies used to select which products to develop and when. Furthermore, investigations have been made to compare the success of compounds developed within firms' alliances, *versus* those developed by single firms [10,11].

No specific effort, however, appears to have been made to isolate those determinants affecting the decision by large firms, to allocate early stages to other, often smaller, companies, rather than developing the whole process in-house. Factors that might help explaining such a phenomenon could also be a decrease in venture capital funding to early stage biotech firms, as well as the need, for large companies, to fill drug development pipelines [2,10]. Our starting point in this article is that whatever the reason, strategic advantage, that may support alliances, the very definite motivation must be driven by profitability considerations.

Based on this last consideration in the paper we attempt to contribute to the understanding of such stage division, focusing on the role of the stage success probabilities in determining the allocation of the various development stages. In particular, we examine an intuition that would naturally suggest that small companies develop the early stages of the process, only if they are more suited than large firms in dealing with that kind of initial risk.

In order to do so we concentrate on the following simple, yet sufficiently rich, stylized scheme. Let us suppose (with no mean-

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ingful loss of generality) that a drug development process is composed of two stages, stage 1 and stage 2. We could think of such two stages as parts, or aggregations, of the various drug development phases. The compound will be eventually commercialized only if both stages are successful; therefore, stage 2 will take place only conditional upon stage 1 having been successful. Moreover, suppose that initially there are two firms: firm A is a small company endowed with limited resources that could only allow it to pay for the costs of stage 1, while firm B is large enough so as to be able to undertake both stage 1 and 2 in-house, or only one of them. A generalized version of the model could also consider alliances between two large firms, but our interest in this article is to isolate the conditions under which a big company may find it convenient to delegate to a small (financially less endowed) firm parts of a drug development process.

Therefore, the two stages of the drug development process can be seen as a sequence of two 'success or fail' types of random experiment. Of course, in reality, failure may not be complete: compounds which eventually do not reach commercialization may still be useful in fostering the understanding and development of other compounds. Yet to simplify the exposition, still without much loss of generality, we assume the experiments can have only one of the two possible outcomes.

Though the experiments are random, however, the way firms interpret success probabilities could differ. In this article we shall consider two possible interpretations of the relevant probabilities: they can either express (i) a firm degree of pessimism–optimism on the success of a stage, independently of which firm is in charge of that stage or (ii) the ability of a company in undertaking a given stage. Though conceptually different assuming firms to be risk-neutral, in that they intend to maximize their own expected payoff, the two probability interpretations will lead to similar results.

Below we start the exposition considering the development of a single pharmaceutical, as a benchmark case; the analysis will then be useful for the main conclusion of the paper.

One pharmaceutical with 'firm-independent' success probabilities

Suppose p_A and p_B indicate the success probability of stage 1, for firm A and company B, respectively, while q_B the success probability of stage 2 for firm B, conditionally upon stage 1 having been successful. In this first interpretation firms can have different probabilistic views that, however, do not depend upon which company is running the stage, but rather by the perceived intrinsic difficulty of obtaining success in a particular stage. This means, for example, that for firm A the stage 1 success probability p_A is the same whether A, instead of B, develops that stage. An analogous interpretation holds for p_B. In this sense, probabilities could be interpreted as the degree of optimism–pessimism that companies have on the possibility of success, and in this interpretation would be viewed as firm-independent.

Furthermore suppose that C_1 and C_2, with $C_1 < C_2$, are the monetary costs companies have to pay to conduct stage 1 and 2, respectively, and that R_2 is the revenue accruing to firm B should the drug be successfully commercialized. To simplify, we begin by assuming that the cost of a stage is fully borne by the firm running that stage. A short discussion concerning cost sharing of the first stage is postponed until the last section of the article.

Finally, if firm A successfully develops stage 1 it will sell at a price R_1 (contractually fixed by the companies) where $R_1 > C_1$ the outcome of the discovery to firm 2. Moreover, we assume that the sums C_2 and R_1 are available to firm B only in the second stage, conditional on the first stage being successful. We now discuss the conditions under which firm A could find it convenient to develop stage 1, and firm B to either develop both stages fully in-house or only stage 2. Assume the above parameters of the model to be known by the companies, and start considering firm A which, when bearing its entire cost C_1, will find it convenient to develop stage 1 only if its own expected profit

$$E\Pi_A(1) = p_A(R_1 - C_1) - (1 - p_A)C_1 = p_A R_1 - C_1$$

is positive, namely if $p_A > C_1/R_1$.

Analogously, for company B to prefer to develop both stage 1 and 2 fully in-house, rather than not develop them at all, its expected profit

$$E\Pi_B(1,2) = p_B q_B(R_2 - C_1 - C_2) - (1 - p_B)C_1 - p_B(1 - q_B)(C_1 + C_2) = p_B(q_B R_2 - C_2) - C_1$$

must be positive, namely if $p_B > C_1/(q_B R_2 - C_2)$ and $q_B > C_2/R_2$.

Finally, firm B will prefer to develop only stage 2, rather than both stage 1 and 2, if

$$E\Pi_B(2) = p_B(q_B R_2 - R_1 - C_2) > p_B(q_B R_2 - C_2) - C_1 = E\Pi_B(1,2)$$

with $q_B > (C_2 + R_1)/R_2$, implying $p_B R_1 - C_1 < 0$ namely $p_B < C_1/R_1$.

It is interesting to note that to obtain positive profits, in the latter case the more demanding condition on stage 2 probability $q_B > (C_2 + R_1)/R_2$ replaces the weaker requirement $q_B > C_2/R_2$, which is however also accompanied by the condition that $p_B > C_1/(q_B R_2 - C_2)$. This is because when the costs of stage 1 are fully borne by the small company A, all the potential risk of losses for firm B is shifted to stage 2, where the expected return will have to be high enough to compensate for both R_1 and C_2. As a consequence, when company A runs the first stage firm B will only take up, and select, projects with particularly high probabilities of final success.

The above considerations allow the formulation of the following first preliminary conclusion.

Conclusion 1.
With 'firm-independent' stage 1 success probabilities, the small firm A and the large company B will find it profitable to share the two stages of the drug development process, with A developing the first and B the second, only if $p_B < C_1/R_1 < p_A$.

The conclusion identifies the main condition for the firms to prefer to share the development of the two stages. This is due to their having an appropriately different degree of optimism on the success probability of stage 1. In particular, not only firm A should have to be more optimistic than B but, furthermore, the threshold C_1/R_1 must separate their probabilistic beliefs.

Finally, note that $E\Pi_B(2) = p_B(q_B R_2 - R_1 - C_2) > 0$ implies $q_B R_2 - C_2 > R_1$; therefore, except for appearing in the upper bound of R_1, under this interpretation of the success probabilities, no parameter concerning stage 2 enters the decision of having the small company A to develop the first stage. .

One pharmaceutical with 'firm-dependent' success probabilities

Consider now a situation where stage 1 success probability depends upon which firm is running the experiment, and then assume p_A and p_B to be the success probability when, respectively, firm A and firm B is in charge of that stage. In this case probabilities formalize the firms' efficiency in running the initial stage. Then, while the condition for company A accepting to develop the early stage remains as $p_A > C_1/R_1$, the requirement for firm B preferring to develop only stage 2 now becomes

$$E\Pi_B(2) = p_A(q_B R_2 - R_1 - C_2) > p_B(q_B R_2 - C_2) - C_1 = E\Pi_B(1,2)$$

with $q_B > (C_2 + R_1)/R_2$, $p_B > C_1/(q_B R_2 - C_2)$, where the main difference with respect to the previous formulation rests in the probability p_A, rather than p_B, now multiplying $(q_B R_2 - R_1 - C_2)$.

The above inequality is satisfied if

$$p_A > \frac{p_B(q_B R_2 - C_2)}{(q_B R_2 - R_1 - C_2)} - \frac{C_1}{(q_B R_2 - R_1 - C_2)}.$$

Note that the expression $p_B(q_B R_2 - C_2)/(q_B R_2 - R_1 - C_2) - C_1/(q_B R_2 - R_1 - C_2)$ is linear in p_B, has negative vertical intercept, slope greater than one, and crosses the identity function p_B from below at $p_B = C_1/R_1$. Moreover, at $p_B = 1$ the function $p_B(q_B R_2 - C_2)/(q_B R_2 - R_1 - C_2) - C_1/(q_B R_2 - R_1 - C_2)$ is greater than 1 which means that company B could accept stage division only if $p_B < 1$, namely if p_B is not too high.

Since C_1/R_1 represents also the lower bound to p_A, for A to accept entering the contract, it is easy to see that both firms would find it convenient to enter a written agreement allocating stage 1 to company A only if $p_A > p_B$. However, as well as with the firm-independent probabilities interpretation, this is a necessary though not a sufficient condition for stage division, since there could be probability pairs $p_A > p_B$ such that either firm A would not want to enter the contract, or firm B would prefer to run both stages. Therefore, the small firm A must be appropriately more skilful than B in running stage 1: this is summarized by the following, second, preliminary conclusion.

Conclusion 2.
With 'firm-dependent' stage 1 success probabilities, the small firm A and the large company B will find it profitable to share the two stages of the drug development process, with A developing the first and B the second, only if p_A is greater than C_1/R_1 and sufficiently higher than p_B, and p_B is not too high.

It is interesting to note that Conclusion 2, unlike Conclusion 1, allows for p_B being greater than C_1/R_1, as long as the other conditions are satisfied.

To summarize, the above two findings suggest that in a single project, independently of the interpretation of stage 1 success probability, there could be no stage division between the two firms when the large company is more optimistic, or more efficient, than the small firm in developing the first stage.

Therefore, if this conclusion seems to confirm the intuition under examination, below we discuss how, with more than one potentially interesting project to develop, when the large firm is resource-constrained and can not fully develop in-house all the potentially profitable projects, then there could be stage sharing even when the large firm would be more suitable in running both stages.

Two pharmaceuticals and no resource constraints for the large firm

In what follows we consider two probabilistically independent projects, I and II, two small firms A and A*, and one large firm B. Both projects, as in the previous case, consist of two stages, 1 and 2, with $p_A = p_{A^*}$.

Begin by assuming that the large company B has no constraints on resources, which means that it could develop fully in-house projects I and II, or alternatively allocate one or both the initial stages to the small firms, if more profitable. Then B would decide which stages, of what projects, to develop by simply examining the economic convenience of I and II separately, namely evaluating their profitability independently of each other, whatever the interpretation of stage 1 success probability. This implies that with no resource constraints stage 1 of both projects will be allocated to small companies only *if* A and A* are more efficient, or more optimistic on success, than firm B.

Two pharmaceuticals and resource constraints for the large firm

Suppose instead that now firm B has limited resources, and could only fund either a single project completely in-house or, alternatively, stage 2 of both projects I and II. The extent to which financial constraints could affect large firms R&D expenditures has been investigated in the literature [12,13], with respect to US and Japanese firms, though the issue remains an open question. In what follows we discuss how in the simple case of identical projects firm B could find it optimal to allocate stage 1 to each of the small firms, even if B would be more efficient, or optimistic, than A and A* in developing stage 1 of the two projects. Before proceeding it is worth pointing out that focusing on independent and identical projects does not limit the generality of the conclusions, and that these assumptions are introduced only for convenience of illustration.

Begin by interpreting probabilities as being firm-independent, namely as their own degree of optimism on stage 1 success. Then, under the assumption of identical and independent projects, when allocating stage 1 to small firms, at the previous contractual conditions, company B's overall expected profit is

$$2\,p_B(q_B R_2 - R_1 - C_2)$$

Therefore, while small firms A and A* would be willing to enter an agreement with firm B if still $p_A = p_{A^*} > C_1/R_1$, the large firm would now prefer to develop only stage 2 of both project I and II when:

$$2\,p_B(q_B R_2 - R_1 - C_2) > p_B(q_B R_2 - C_2) - C_1$$

namely, if $p_B(q_B R_2 - 2R_1 - C_2) > -C_1$. Clearly, if $(q_B R_2 - 2R_1 - C_2) > 0$ then any p_B satisfies the previous inequality which, as for stage 1 success probability, would allow for firm B to be more optimistic than the small firms. But since $C_1/R_1 < C_1/[2R_1 - (q_B R_2 - C_2)]$, even if $(q_B R_2 - 2R_1 - C_2) < 0$ there could be probability levels p_B, between C_1/R_1 and $C_1/[2R_1 - (q_B R_2 - C_2)]$, such that A, A* and B would find it convenient to share stages 1 and 2, with the large firm being more optimistic than the small companies.

TABLE 1

Stage division, with firm-independent probabilities, when the large firm is more optimistic than the small companies on the success of the first stage

	p_A	p_B	R_2	R_1	C_2	C_1	q_B	$E\Pi_B(1,2)$	$E\Pi_B(2)$
Project I	2/5	1/2	1000	40	20	10	1/2	230	220
	p_{A^*}	p_B	R_2	R_1	C_2	C_1	q_B	$E\Pi_B(1,2)$	$E\Pi_B(2)$
Project II	2/5	1/2	1000	40	20	10	1/2	230	220

Suppose now probabilities formalize the firms efficiency in running stage 1. Then, following similar assumptions, firm B would prefer allocating stage 1 of both projects to A and A^* if

$$2p_A(q_BR_2 - R_1 - C_2) = 2p_{A^*}(q_BR_2 - R_1 - C_2) > p_B(q_BR_2 - C_2) - C_1$$

which can be satisfied for values $p_A = p_{A^*} < p_B$, even though this would imply that, with no resource constraints, running both projects fully in house would be preferable for the large firm.

Table 1 presents a numerical example illustrating such possibility, based on firm-independent probabilities.

The two projects in Table 1 are such that $p_A = p_{A^*} < p_B$ and so for firm B, in a single project, it would always be convenient to run both stages. Resource constraints however will not allow company B to do so; therefore, in deciding where to invest it would then compare the best single project outcome, namely 230, with the sum of the expected payoffs when running only stage 2 of both projects, namely $220 + 220 = 440 > 230$. Since 220 is slightly lower than 230 it would turn out to be profitable for firm B to allocate stage 1 of both projects to the small companies, even if they are less efficient.

We can now state the main conclusion of the paper.

Conclusion 3.
When the large firm has enough resources to develop in-house all potentially interesting projects then there could be stage division only if small companies are more efficient, or optimistic, in running the early stage. When the large firm has limited resources, however, and cannot develop fully in-house the two projects, then it may prefer to agree with the small companies that they should develop stage 1 of the two projects after which, if successful, B would develop stage 2 of both projects, even if $p_{A,} = p_{A^*}$ is lower than p_B.

Social desirability of stage division

So far we have only focused our attention on a drug development process stage division from the point of view of the individual companies. In this section we briefly discuss if, and when, stage division could also be socially, and not just individually, desirable. Clearly, in order to do so we first need to introduce a notion of social welfare. A common way, though not the only one, to formalize social welfare is to sum the firms' expected profits. If we do so, in the case of one pharmaceutical, we immediately obtain the following conclusion.

Conclusion 4.
With one pharmaceutical, if firms A and B find it profitable to share stages of a drug development process then this is also socially desirable.

The above conclusion, which holds independently of the interpretation of probabilities, is based on the following simple argument. When firms agree to share stages of a drug development process, then the small company A will obtain strictly positive expected profits, as opposed to zero profits should the alliance not take place, while the large firm B profits are higher than the ones obtainable if the two stages of the drug development are carried on fully in-house.

By a similar argument it follows that social desirability of alliances also holds in case of two pharmaceuticals, however with the proviso that in some situations social desirability may be explained by the large firm being resource constrained, and that in case its resources were not limited stage division could be socially undesirable.

First stage cost sharing

Would conclusions change if large companies were willing to pay for some of the first stage costs? In this section we briefly discuss how previous conclusions might change if first stage costs, and risk, are shared focusing only on one pharmaceutical with firm-independent success probabilities. Analogous considerations could be made for the other cases.

Suppose that, everything else being the same, now αC_1 (with $0 \leq \alpha \leq 1$) is the first stage cost borne by firm A while $(1 - \alpha)C_1$ would be borne by firm B, in case of stage division.

It is important, however, to distinguish the two ways in which firm B could transfer the sum $(1 - \alpha)C_1$ to firm A. Indeed, this could either take place as an upfront transfer of money to A, or else as a transfer occurring only conditional upon successful completion of the first stage. The distinction is meaningful since, as we see below, these two ways of contributing to first stage costs would give rise to different conclusions.

Begin by considering an upfront transfer of money, from B to A: then Conclusion 1 becomes.

Conclusion 1a.
With 'firm-independent' stage 1 success probabilities, if the small firm A pays αC_1 and the large company B pays to A the remaining sum $(1 - \alpha)C_1$ upfront, then the firms will find it profitable to share the two stages of the drug development process, with A developing the first and B the second, only if $p_B < \alpha C_1/R_1 < p_A$.

A way to reformulate the above conclusion is by saying that even if $p_A < C_1/R_1$, as long as $p_B < p_A$ then there always exists a way to share first stage costs, namely a number α, such that it would be profitable for both firms to share the two stages of the drug development process. More explicitly, first stage cost sharing would allow alliances to take place that could not be implemented should the small firm bear the entire cost C_1.

It is interesting to note that if first stage cost sharing implies also that in case of success firm B will pay to A a sum proportionally

lower, namely αR_1 rather than R_1, then Conclusion 1 will remain unaltered.

We now consider B transferring $(1-\alpha)C_1$ to A only upon successful completion of the first stage. In this case Conclusion 1 becomes.

Conclusion 1b.

With 'firm-independent' stage 1 success probabilities, if the small firm A pays αC_1 and the large company B gives to A the remaining sum $(1-\alpha)C_1$, but only upon successful completion of the first stage, then the firms will find it profitable to share the two stages of the drug development process, with A developing the first and B the second, only if $p_B < C_1/[R_1 + (1-\alpha)C_1] < p_A$.

Since $C_1/R_1 \geq C_1/[R_1 + (1-\alpha)C_1] \geq \alpha C_1/R_1$ for all α, from Conclusions 1a and 1b it follows that cost sharing allows company A to be less optimistic, on the first stage success, with respect to when A is bearing the full cost of the stage. In general, and when possible, it may be preferable for B to reimburse A only upon first stage successful completion because this will require a higher degree of optimism by A, with respect to when the sum $(1-\alpha)C_1$ is transferred upfront.

Final remarks

In this article we discussed how a fundamental mechanism explaining why large pharmaceutical firms might prefer to allocate the early stages of a drug development process, to small innovative companies, could be given by an optimal risk and costs allocation among firms of different size. We argued, however, that unlike what the intuition would suggest stage division may not always be determined by consideration related to firms' efficiency, or degree of optimism, on the success of an early stage. In particular efficiency, or optimism, would be the main reasons explaining stage allocation when the large firm has enough resources to fully develop in-house all potentially interesting projects. When a large company, however, is resource constrained and can not develop in- house all potentially profitable projects then it could be optimal for it to have small companies developing the early stage, even when the large firm would be more suitable to run also the initial stage. To conclude, it is expected profit considerations and the large firm availability of resources that would explain whether or not those small companies that are running the initial stages of a drug development process are better suited, to deal with risk in that phase, than large firms.

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