

The Inclusion Of Back-Up Compounds In Pharmaceutical Licensing Agreements

By David Scott

Introduction

Increasingly, before taking on new inward licensing opportunities, pharmaceutical companies are seeking to identify and include back-up compounds, so as to reduce the risk if the lead compound fails in development.

As a result, many of the major companies, such as Astra-Zeneca, now explicitly include the availability of back-up compounds in their set of initial in-licensing evaluation criteria. Indeed, many press releases for reported deals, in particular license agreements between biotech or early stage companies with the major pharma companies such as GSK, Roche and Novartis, now frequently include references to back-up compounds.

This article seeks to review the reasons why companies will wish to include back-up compounds in any license agreement and to set out licensing terms that can successfully incorporate one or more back-up compounds in a way that meets both licensor and licensee needs.

Why Back-up Compounds Are Necessary

From the Licensee's perspective, the primary concern is usually to minimise the risk of failure by having compounds that can "step in" if the lead compound fails.

Products can fail for many reasons, but the most common causes of failure are lack of efficacy or toxicity or safety issues. The risks associated with pharmaceutical products vary depending upon the stage of development and the nature of the likely indication.

To some extent, the various future risks concerned can be evaluated at the time the licensing deal is concluded, and these will have a direct bearing on the deal value. Overall, the levels of risk are very high but decline as development proceeds. Less than 5% of products in pre-clinical development will succeed, but the probability doubles for products in Phase

I clinical development and doubles again to around 20% for products in Phase II clinical development. Once Phase III studies commence, the probability of success rises to between 50 and 70%, depending upon the target indication.

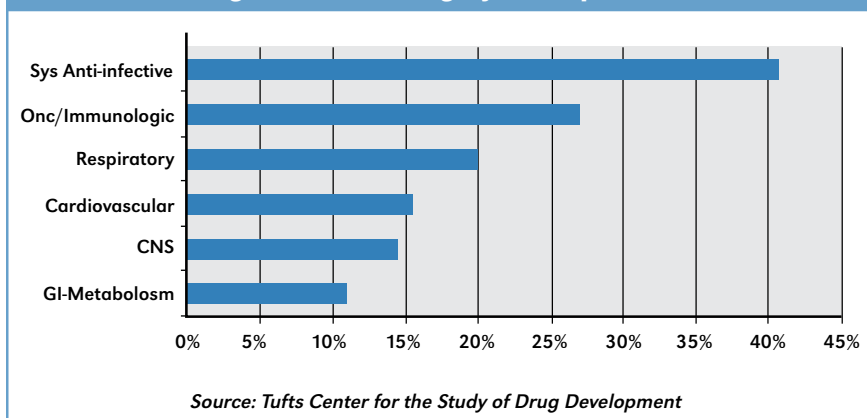
The level of risk will vary from product class to product class, so different indications will carry different perceived levels of risk. Levels of risk for products entering clinical development have been calculated by Tufts Center for the

Study of Drug Development and show significant variations between therapeutic classes in the proportion of drugs entering clinical studies that were able to receive U.S. marketing approval. See Table 1.

These differences are due to a variety of factors relating to the way in which products are developed in different markets and the types of pre-clinical studies available in each case. For instance, antimicrobial products in late pre-clinical will have a low risk of failing from lack of efficacy because pre-clinical microbiological studies are good indicators of the ability to kill bacteria in infections, but will have a higher risk of failing on safety grounds; once Phase II studies are completed, and the safety profile is known, such products are much less likely to fail than drugs in

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Table 1. Clinical Approval Success Rates For Drugs Entering Clinical Testing By Therapeutic Class



other categories. By contrast, in other markets, such as asthma, the profile is harder to establish early on because the available pre-clinical models are much less predictive of efficacy, and the likely competitive clinical profile will not become apparent until Phase III studies are completed.

Poor Phase III results may not prevent a product from being launched, but can significantly compromise the chances of commercial failure, and if heavy launch costs are required, it may simply be too risky to continue.

Other reasons for switching to a back-up may include problems with manufacturing scale-up, formulation or stability. Such difficulties, particularly with stability, may be show-stoppers which make it impossible to continue development or may simply result in higher than expected costs (hence lower profit margins). Hence, there may be a trade-off between continuing development of a high-cost lead product and the additional costs and delays associated with switching to a lower-cost back-up compound. Patent-related issues, such as a failure to obtain a core patent in a major market or freedom to operate issues arising from third party patents, can also be reasons for abandoning a product in development.

Not all the risks are product related. For instance, changes in reimbursement levels or the introduction of novel competing therapies (such as the impact of the introduction of proton pump inhibitors on the market for H2 antagonists) can also impact on the viability of a product in development. However, unlike the directly product-related issues discussed above, such factors will not be ameliorated by the availability of back-up compounds.

When a lead compound emerges from an in-house discovery programme, there are usually many potential alternative products available that could be developed and, as part of the process to establish the lead compound, companies will usually obtain data from a wide range of pre-clinical parameters (such as binding affinity, in-vitro potency, initial toxicity and potential synthesis routes) for a number of promising candidates. This will give the company a good idea as to which products may be most interesting for consideration as back-ups to the lead compound.

Once such potential back-ups have been identified, companies may well undertake some further pre-clinical development of one or more of these so that, in the event the lead compound fails, less time is lost switching to a back-up. Again, the performance of the lead compound may also give some indication of what parameters to seek in promoting a back-up.

For instance, if a lead compound fails because of a production-related problem such as formulation or stability, back-ups can quickly be screened to check for similar problems.

The Role Back-ups May Play In A Licensing Arrangement

Once a product is in-licensed, then the development process for the licensee will follow the same lines as for an internal programme. This means that the licensee will want to be able to consider switching to an alternative back-up compound at any time when a technical or commercial issue arises that brings the viability of the lead compound into question, just as it would in the case of an in-house programme.

In the case of development an in-house product, the company owns all of the back-ups as well as the lead compound. Hence the decision will be slightly different, because the company only has to consider the potential commercial positioning of its lead compound against unrelated competitors. It may well decide that, even if the lead compound is not ideal, it will be better to proceed with this rather than experience the additional cost and delays of bringing forward a back-up.

When a company developing an in-house product based on its own proprietary platform considers the commercial implications, it is safe in the knowledge that it directly controls any direct competition from similar back-up compounds. But what if some of the back-ups are owned elsewhere (as might be the case if the product has been in-licensed from the originator of the platform technology) and might be developed as competitors?

In this case, even though it will increase the costs, it may make more sense to switch development to a product offering a better profile so that, when it is launched, its commercial position is not damaged by the entry of a compound from the same family being developed elsewhere.

Hence, a licensee will consider the availability of back-ups not just from the perspective of replacing a failed lead compound, but also from the point of view of enabling or preventing competition from similar products. This means that, in addition to concerns over the likely success of the lead compound, licensees may also be keen to secure rights to as many compounds in the family as possible so as to ensure these do not become competitors to the main licensed product.

So, ideally, the licensee would like a broad range of back-up products included in the license agreement at no additional cost in a way that allows it the free-

dom to develop these as and when it wishes, but with no obligations to do so if the lead compound is successful.

From the perspective of the licensor, things are rather different. Although the licensor may be willing to include back-up compounds in the agreement to allow substitution in the case of the failure of the licensed product, more often than not the licensor will be hoping to exploit at least some of these back-up compounds in different markets.

This may take the form of developing distinct formulations for use in different therapeutic sectors (perhaps developing one product for ophthalmic use, another for inhalation) or for veterinary rather than human use. If the class of molecules or platform concerned has activity in a variety of different indications, it may be that these can better be exploited via different compounds and via different partners rather than by using just one molecule. Of course, the licensor may even be hoping to develop or license one or more of the back-ups as a direct competitor to the lead compound!

Against this, the licensor will of course be keen to encourage the licensee to succeed, so will be willing to make back-ups available, in the hope that if the lead compound fails, the licensee will be encouraged to try again—after all, if the licensed lead compound fails completely the back-ups will be worth a lot less to other potential licensees.

From this it is clear that the licensor will be willing to offer back-ups, but in so doing will want to retain some flexibility regarding how these can be exploited or will want the deal to reflect their potential value.

These partially conflicting objectives for the licensor and licensee suggest that back-up compounds do indeed need to be included in most agreements, but in a way that provides flexibility and that gives the licensee security at low additional cost yet lets the licensee profit from their potential value.

Incorporating Back-ups In Licensing Agreements

So how should back-up compounds be included in licensing agreements?

In agreements where the full range of compounds included in the platform are all covered by one or more patents, then one option would be for the license grant to simply refer to the patent and grant the licensee rights to all compounds covered by the patent. This would of course be ideal for the licensee, who would then control all of the products likely to emerge from the platform. However, this would

mean that the licensor would be unable to exploit its technology elsewhere, and unless the deal fully valued all the potential products that might emerge, is unlikely to give the licensor fair value.

Of course, an easy alternative would be to include the back-up compounds within the definition of product, so that all the potential back-ups are treated in the same way as the lead compound. In this case, the licensor could specify a range of back-up products, whilst keeping some in reserve for use elsewhere. The difficulty with this approach lies in the conflicting objectives of the licensee, who will want as broad a range of back-ups as possible, ideally at no extra cost, and the licensor, who will want a very narrow list of back-ups unless the licensee is prepared to compensate the licensor via higher up-front payments for not having these for use elsewhere.

What is really required is a structure that allows the licensee the freedom to select the best possible back-up if the lead compound fails, but in a way that doesn't force it to pay a premium for the back-ups unless they are required. Ideally, the structure should make it possible for the licensee to "buy-out" potential competition from back-ups by including these, but only by paying the licensor fair (i.e. significant) compensation, something the licensor is only likely to be able or willing to do once it is sure the product is likely to succeed.

Option Agreements

So, whilst back-up compounds could be included in the licensing agreement itself, a better route would be to include them under some form of option agreement. This would allow both parties to act independently once the option expires, and could allow for different payments by the licensee depending upon what circumstances prevailed at the time it was exercised.

In its simplest form, an option could take the form of the right to take a license on the back-up within a set period (say 2 years) in exchange for an up-front fee once the option is exercised, followed by milestones and royalties similar to those in the original license agreement.

If only life was that simple! In practise this would cause both partners some problems, not least because the value of the back-up would be fixed without knowing why the back-up is required. Clearly, if the back-up is required to replace a failed lead compound, it should have less inherent value than if it is being licensed as a result of the successful development of the lead compound.

It is always possible to include an option to license

the back-up under terms to be “negotiated in good faith, reflecting the relative value of the product at that time.” But any agreement to agree (even with defined “first refusal” rights) can be risky and is no substitute for a properly valued agreement.

Reasons For Exercising An Option

The best solution is to think about how, and why, the licensee would wish to exercise the option and to pre-set terms that reflect these reasons. The most likely causes for wanting to exercise the option will be:

a) A problem arises with the initial product which is seen as being specific to that product, rather than a class effect. Hence the licensee would wish to continue development, but with a back-up compound that avoids whatever the problem was.

b) The licensee wishes to ensure that in the event that a back-up is necessary, time is not lost catching up. This means someone must be continuing development work on the back-up whilst development of the lead, licensed, compound continues.

c) The licensee decides that the potential market can be exploited more effectively by developing different products for different indications. This may be due to formulation limitations with the licensed product (for example, if it can only be administered in an IV form) or simply because different products would better meet any marketing plans.

d) The licensee wants to prevent a competitor from entering the market with a similar product, such as may be represented by the back-ups if licensed to someone else (or launched directly by the licensor).

These options are listed in order of their potential value. If the lead, licensed compound has failed, then a back-up should be available at little or no additional cost. If the licensee simply wants to extend the value of the license or restrict competition via a license of the back-ups, then this has a price in terms of what the licensor might have been able to do with these additional products elsewhere, and this price should be reflected in any option payments.

When a product is licensed at a very early stage, then success of the licensed product will add value to similar compounds in the licensor’s portfolio. Whether or not these are included within the licensing arrangement as back-ups, the licensee may take the view that some of this added value is down to its development activities, and if the licensor is to profit from these products elsewhere, some of this added value should accrue to them. Hence, agreements may sometimes include some form of cross-royalty, under which the original licensor pays the licensee a share of any net income received on the subsequent

exploitation of other products in its portfolio.

When The Licensed Compound Fails

Of course, substituting a failed lead (licensed) compound will always be the main reason for needing to include back-ups. In this case, it is in both partner’s interests that the process is as speedy and painless as possible.

The decision to abandon the lead compound is one that should be made primarily by the licensee, who is after all the one investing resources on its development; but ideally both partners need to accept that the lead product has failed. Sadly, in many cases, the licensor finds it hard to agree with its partner that the product has indeed failed, and this can lead to an acrimonious debate.

This acrimony can be avoided, at least in part, if the licensee is required to hand back not only the product rights, but also all of the data it has generated in the course of ongoing development for the licensor to do with as it sees fit. In this case, the licensor will then be free to develop the product itself (or to license it elsewhere) if it believes the licensee was wrong, without having to repeat all the studies undertaken by the licensee. For its part, if the licensee is genuine, it will know that the product has no value, and will be happy to comply.

In this case, the back-up should be made available at little extra cost to the licensee, and is in effect an exchange of products—the licensee gives back the originally licensed product in exchange for the back-up. In the event that the licensee remains uncomfortable about handing back what might be a substantial body of work, a sensible compromise may be for the licensor to have the right at its option to take back the work undertaken by the licensee in exchange for a payment. The amount of this payment could be pre-agreed, or to be determined by a mutually agreed independent valuation. If the licensee wishes to continue the development, it will need to pay this to the licensor to have access to the data; if it doesn’t want the data it would be free to decline.

If the licensee wants the product for other reasons, be they to extend the market or to limit competition, then the cost should be much higher. However, exact motives may be hard to prove. So again, the key issue is whether or not the licensee is willing to hand back the original product. If not, then the price to be paid can be set to reflect the assumption that licensing the back-up will provide added revenue for the licensor.

But what if the licensee simply wishes to take out potential competition? In that case, the licensee

may simply exercise the option and then sit on the product. To prevent this, the agreement will need to include development timetables, and require the licensee to make penalty payments or return the product if these are not met. Such penalties can be allowed to escalate to reflect the lost value to the licensor. The licensee may not like this, but can at least make a rational decision on whether or not to pay the penalty or allow the product to revert to the licensor—clearly it would only pay the penalty if it thought this was justified by retaining control of the back-up.

The Timing Of An Option

The timing of the option needs to reflect the likely timescale for development of the lead compound to a point where a back-up is not appropriate. Clearly, the licensee will want this to be as long as possible (probably up to first launch), but the licensor will want to have the chance to develop or license its back-ups elsewhere earlier than that.

A sensible compromise is to extend the option to the point at which the first pivotal Phase III clinical trial is expected to have been completed, as at that point the competitive profile of the product will be broadly established and the risk of obtaining a product registration will have been much reduced. A deadline date to achieve this after allowing time for reasonable delays should be mutually agreed, and can set a sensible time period for any option.

The option itself should be set against a specific date, not a milestone, so that if the licensee takes longer over development it will have to decide whether or not to risk letting the option lapse. This will act as an added incentive for it to expedite the development programme!

The option period could of course be extended at the licensee's option in exchange for an additional fixed payment.

Development Of Back-ups

For an internal development, it is likely that some development work would be carried out on back-up compounds in parallel to the development of the lead compound so as to minimise any delays if the lead product fails. Making sure the back-ups are developed as part of an option agreement is clearly more complex, and there are a number of ways this can be achieved:

a) The licensee could exercise the option early and develop the back-up itself in parallel to the development of the lead compound. However, as the licensee would not wish to relinquish the lead product, exercising the option would probably be expensive.

b) The option agreement could grant the licensee the right to undertake further development itself, recognising that if it failed to exercise the option any development work it had undertaken would revert to the licensor.

c) The license deal could include a requirement for the licensor to undertake continued development of one or more back-ups. The cost and benefits to the licensee from this may be reflected in a higher up-front payment and/or higher fee on exercising the option, and may also be reflected in milestone payments against development of the back-up as an incentive to speedy completion.

d) Alternatively, at its option, the licensee could pay the licensor as a sub-contractor to undertake such work on its behalf.

The Deal Structure

So, as well as a license agreement for the lead compound, an ideal arrangement might be expected to include an option agreement for a range of possible back-up compounds. These are essentially separate, stand alone agreements that will be executed simultaneously.

The License Agreement

This will include whatever up-front, milestone and royalty payments are considered appropriate for the product on a stand-alone basis, along with usual terms for the other elements of the deal. This agreement should, however, also include target dates for key milestones, in particular for completion of the trigger-point for termination of the option (probably completion of the first pivotal Phase III trial).

Termination clauses will need to include termination (at the licensee's discretion) upon the exercise of the option, under terms that provide for all IP rights in the product and all development carried out by the licensee to revert to the licensor for no payment (or possibly for a nominal pre-agreed amount depending upon the amount of development undertaken by the licensee).

The Option Agreement

The option should grant the licensee in-license rights to one or more molecules (to be selected by the licensee from a named list) on terms set out in an appended license agreement. Alternatively, the option could cover all molecules included under the same patent as the licensed lead compound.

The option will terminate on a specific date or require the licensee to make an additional payment to extend it for, say, an additional year. This date is likely to reflect the time required to reach a certain

development milestone, so its length will depend on the stage of development of the lead product at the time the initial agreement is signed. However, the time period of the option will be a set period (probably a round number of years) rather than be dependent on actual completion of parts of the programme.

On termination of the option, the licensor would be free to do whatever it wished with the back-up products (such as licensing them elsewhere).

The appended license agreement should contain broadly identical terms to the original license agreement, but with different payment terms and milestone timings.

Payment terms should depend on what happens to the initially licensed product, and should differ in the case of when the original license agreement terminates (which implies the lead compound is being replaced by the option product) and for when this carries on (which implies the option product is being developed in addition to the original compound).

Of course, the licensor may decide it will only offer back-up compounds on the basis that the licensee can only access a back-up by terminating the original agreement, but this is less likely to be attractive to most big pharma partners.

Terms For When The Original Agreement Terminates

If the licensee elects to terminate the original license agreement, then up-front payments on exercising this new license agreement will be nominal (i.e. less than the original up-front) and milestone payments will reflect those in the original agreement. The wording should make it clear that any milestones that have already been paid by the licensee under the original license agreement will not have to be paid a second time for development of the back-up product. This means that milestone payments will ladder from the point reached in the original development programme before the lead compound was abandoned, so that the licensee will pay future milestones. Royalties will be paid on the same basis as set out in the original agreement. Similarly, any timetables set out in the original agreement should ladder from the date the option is exercised.

Terms For When The Original Agreement Continues

If the original license is not to be terminated, then there should be a full set of additional up-front and milestone payments for the back-up license which should be comparable in magnitude to the amounts set out in the original agreement. Milestone payments already made or due in the future will not be offset

against those in the new agreement as the license is in effect for an additional product. Royalty rates should remain the same rate in both agreements as this is paid on sales, and both products will generate their own independent revenue streams. Any timetables again should not directly relate to the initial product agreement, but should reflect similar timescales from the point of development of the back-up at the time the option is exercised.

Because the back-up is not replacing the lead compound in this scenario, the agreement should require the licensee to undertake development of the back-up as well as of the original product. The agreement should include some form of penalty against the licensee's failure to sustain development of the back-up. The most appropriate penalty would be a minimum annual payment that remains nominal during development, but that escalates in line with expected royalty streams from the anticipated target launch date. This would still allow the licensee to prevent a third party from developing the product without necessarily developing it itself, but at a price that would remove any incentive the licensee may have to "sit on" the product rather than allow it to revert to the licensor. Hence, these minimum annual payments should at least partially reflect the opportunity cost to the licensor of not having the product available to license elsewhere.

The licensee would be free to terminate the agreement at any time, provided that the original intellectual property along with any development work then reverted to the licensor. In this case, it would be reasonable to allow for some payment to reflect any added value from the licensee's development programme.

Additional Option Products

This higher-value agreement should also be applied to any additional back-up products taken up by the licensee, whether or not the original product license is terminated.

Development Of Back-Up Products

The option agreement should also address how continued work should be undertaken on the listed back-ups. The best approach might be to allow the licensor to undertake any reasonable development of the back-up products it felt desirable at its own expense (but subject to the reasonable agreement of the licensee) and for the licensee to be entitled to fund additional work it deemed appropriate through sub-contractor payments to the licensor, who would undertake the work. Ownership of the additional work would remain with the licensor (whoever

instigated or paid for it) but would transfer (at no additional cost) on exercise of the option for the product concerned. Thus neither party would be obliged to fund work during this time, but either could do so if they so wished.

Summary

This article has set out some of the main issues related to inclusion of back-up products in a licensing agreement, and proposed a balanced deal structure to allow their inclusion without benefitting or disadvantaging either the licensor or the licensee. This is achieved via an option agreement with terms for the licensing of the back-ups that differ depending on whether or not the licensee wishes to retain the original product, or is willing to hand this back to the licensor. The various option scenarios are summarised on the box below. ■

Summary Of Deal Structure For A License Deal Including An Option To Back-Up Compounds

Licensor grants license for lead compound and an option on selected back-up compounds. Option agreement to set out terms of a license agreement for the products included. Thereafter one of the following scenarios will arise:

- **Licensee continues to develop the lead compound and the option lapses** after fixed period. Licensor free to do whatever it wishes with the back-up compounds.
- **Licensee abandons lead compound and exercises the option** to take on a back-up compound for a nominal additional payment, continuing development and future milestones under terms similar to the original license agreement. **Rights to the originally licensed lead compound revert to the licensor** (including to development work undertaken by the licensee up to the exercise of the option), who is free to do whatever it wishes with the original product.
- **Licensee continues to develop the lead compound but exercises its option on one or more back-ups.** Separate license agreement executed (with terms set out in the option agreement) for the back-ups, which will include **significant up-front and additional milestones** (similar in magnitude to those paid or due for the original product). Terms would **require licensee to develop**, with rising annual **minimum payments to compensate the licensor** if development is not forthcoming.

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