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Correlated Milestones

Over Christmas we have asked our readers to value a relatively common license clause that reads as follows:

- 3 compounds.
- They are all based on the same technology and therefore correlated (rho=50%).
- Each compound has a probability of success of 30%.
- Compound 1 could reach the market in 3, compound 2 in 4, and compound 3 in 5 years.
- For the first approved compound you receive a milestone of USD 30 mn, for the second USD 20 mn, and for the third USD 10 mn.
- We use a discount rate of 15%.

What not to do, part 1

A straightforward reaction would be to attribute the first milestone to the first compound, the second to the second, and the third to the third. Each milestone therefore has a probability of 30%, overall the value would be USD 10.8 mn.

Clearly, this valuation falls short of the intention that if any milestone is to be paid, it is first the largest one of USD 30 mn.

What not to do, part 2

The difficulty is that we cannot immediately attribute a probability and a time to the three milestones. The easiest is the third milestone, which is only received if all three compounds reach the market and therefore coincides with the approval of the latest compound in 5 years. But already the milestone for the second approved compound is either paid out in 4 or in 5 years, depending on which compounds reach the market. For the milestone of the first approved compound it is even more complicated, because it might happen either after 3, 4, or 5 years. In total 8 scenarios are possible ($8=2^3$). For each scenario we can determine, when the milestones are due as displayed in table 1.

Table 1: Possible scenarios.

Compound 1	Compound 2	Compound 3	Milestone 1	Milestone 2	Milestone 3
1	1	1	3	4	5
1	1	0	3	4	-
1	0	1	3	5	-
0	1	1	4	5	-
1	0	0	3	-	-
0	1	0	4	-	-
0	0	1	5	-	-
0	0	0	-	-	-

Assuming that the compounds are independent of each other we can easily determine the probabilities for each scenario.

Table 2: Probabilities fort eh independent case.

Compound 1	Compound 2	Compound 3	Probability
1	1	1	2.7%
1	1	0	6.3%
1	0	1	6.3%
0	1	1	6.3%
1	0	0	14.7%
0	1	0	14.7%
0	0	1	14.7%
0	0	0	34.3%

With these probabilities we can risk-adjust and discount the milestones. The value is USD 14.1 mn. However, we have not considered that the compounds are correlated. This means that if the first compound passes, it is likely that the others pass as well and vice versa. The diversification effect is reduced, i.e. the probability that at least one compound gets approved is smaller than if they were independent of each other. This means that the probability of getting the USD 30 mn is reduced while the probability to receive the smaller milestones is increased.

Probabilities

If there were only 2 compounds, the probabilities of the $2^2=4$ scenarios would be easy to determine using the four conditions that a) all probabilities add up to 100%, b) compound 1 has a success rate of 30%, c) the same for compound 2, and d) that they are correlated by 50%. We have four conditions for four unknowns.

Table 3: Possible probability distributions.

Compound 1	Compound 2	Probability rho=0%	Probability rho=50%	Probability rho=100%	Probability rho=-43%
1	1	9%	19.5%	30%	0%
1	0	21%	10.5%	0%	30%
0	1	21%	10.5%	0%	30%
0	0	49%	59.5%	70%	40%

Note that a complete negative correlation is not possible, because that would mean that no simultaneous events, also simultaneous failures are possible. This can only work with 50% success rate.

For the case of three compounds the situation is a bit more complicated. There are 8 possible scenarios as lined out in table 1. But we have only 7 conditions; the probabilities must add up to 100%, the success rates of all 3 compounds must equal 30%, and the pairwise correlations must be 50% (1+3+3 conditions). This means that we have another degree of freedom. Table 3 displays 3 probability distributions that comply with the problem setting, any interpolations are also valid. For continuous random variables these different joint probability distributions are summarised under the topic of copulae.

Table 4: Possible probability distributions.

Compound 1	Compound 2	Compound 3	Possibility 1	Possibility 2	Possibility 3
1	1	1	9%	16.4%	19.5%
1	1	0	10.5%	3.2%	0%
1	0	1	10.5%	3.2%	0%
0	1	1	10.5%	3.2%	0%
1	0	0	0%	7.4%	10.5%
0	1	0	0%	7.4%	10.5%
0	0	1	0%	7.4%	10.5%
0	0	0	59.5%	52.2%	49%

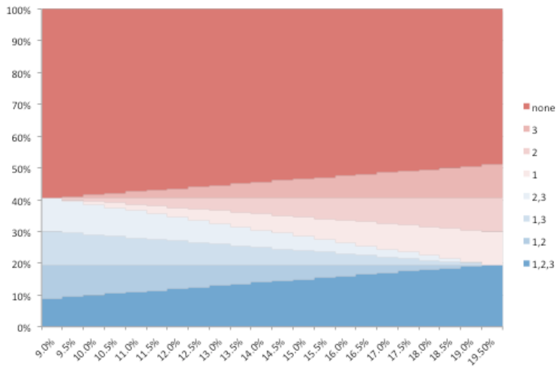

Figure 1: Different probability distributions that comply with the conditions.

Valuation of milestones

With table 1 and 4 (or figure 1) we can now calculate the value of the milestones.

Interestingly, the value is for any probability distribution USD 12.5 mn (the solution to our Christmas valuation riddle). This is, however, a pure coincidence due to the weights of the milestones. If there was only the first milestone, and the others are put to zero, then the value would range from USD 7.7 mn to USD 9.3 mn, a difference of 20%. So the difference arising from the choice of the probability distribution (in figure 1) can be considerable. Obviously the same effects can also be observed in the royalty calculation, even though to a lesser extent.

Other methods

Milestones and royalties for various compounds (or indications) are not easy to handle. One usually has to model the various possible scenarios; for n compounds these are 2^n. Assuming, as is conceivable for platform deals, various projects with several indications, matters complicate further. 5 projects with 3 indications each lead to 2^{15}=32,768 scenarios. A clean valuation would be quite cumbersome.

A straightforward method to tackle the problem is via Monte Carlo simulations, where the milestones can be programmed relatively easily. The value is subject to some natural noise due to the random nature of the simulations, but can be contained by increasing the number of simulations.

It has been proposed to model the similarity of the projects in a different way. One could increase the success rates of a project as soon as it is known (in the valuation timelines) that the previous project has passed, and vice versa. It then remains to be discussed by how much. These changes correspond in principle to a correlation between the compounds. We have chosen to define correlations as this is a mathematically standard definition of resemblance of random variables.

In the problem we had the luxury of dealing with just one overall success rate that was the same for all compounds. In reality we might have various success rates (e.g. for phase 2, phase 3 and approval) that aren't even the same for all compounds (maybe we have oncology and autoimmune compounds). In these cases Monte Carlo simulations might be the best route as a simple rule to in- or decrease the probabilities is easier to implement than to look for probability distributions that correspond to certain correlations over various phases.

Conclusion

We have seen that a relatively standard definition of milestones can cause quite a lot of problems in the valuation. If milestones are defined for first, second, etc. indications or projects to reach a certain stage we have to consider that the time of these milestones depends on the indication or project that triggers the milestone, which is not a priori known. Furthermore, we need to consider that the indications or projects have some similarity and cannot be treated as independent events. We have shown that value differences due to wrong interpretation or implementation can be considerable. It is difficult enough to estimate all the hypotheses that surround a drug development project. At least the way from hypotheses to value should be without mistakes. But this way is sometimes more difficult than thought.