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Success rates, transition probabilities, phase 2a and 2b.

Success rates vs. transition probabilities

At the very beginning we need to clarify the term "success rate". *Success rate* is a statistic measure of how many projects have reached commercialisation out of a certain sample. These samples are typically chosen as projects entering phase 1 during a period sufficiently in the past such that by now we should know the final fate of each project. In contrast to the success rates *transition probabilities* are statistical measures of how many projects having entered a certain phase and have been continued in the next phase. There are various methods of assessing success rates and transition probabilities, the difference being the inclusion criteria in the samples and how to deal with projects whose fate is not yet known (still in development).

Unfortunately it is not necessarily true that the multiplication of all transition probabilities equals the success rate. The reason for this is that there are differences over periods of time. These can have various reasons. First, we can think of new technologies. The first monoclonal antibodies achieved fabulous success rates, while the later ones then had to address more difficult targets and lead to more failures. Second, changes of the regulatory environment like, e.g., after Vioxx, can lead to less positive results. Third, it is also simply possible that in one period the R&D success is better than in another period, just the same way that it is possible to roll 10 times a 6 with a dice. The transition probabilities are not constant over time, but they have a certain term structure. Analysts within pharma companies, scientists, and portfolio managers try to figure out which disease area or mechanism of action provides the best chances of success in the future. They try to extrapolate some trends of the past transition probabilities (actually observed successes and failures in the past) for the future.

Success rates in valuation

In valuation we actually use transition probabilities. However, they are almost always referred to as success rates. We at Avance are no exception. The idea of rNPV is to adjust each cash flow with probability that it occurs; or in other terms, to probability-weigh all possible scenarios. By using the transition probabilities we can differentiate the cash flows of each different R&D phase, and we use for each phase the most recently observed results, which – this is the idea – is most predictive for the probabilities in the future. On the flip side transition probabilities for different phases necessarily are based on different projects, stemming from different periods, with different best practices. But for the moment it seems to be the best solution.

Phase 2a and 2b

As if all this weren't confusing enough, drug development now not necessarily follows the same pathway as the structure of the transition probabilities, i.e. phase 1, phase 2, phase 3, and review phase. It has become increasingly common to split phase 2 in a phase 2a and a phase 2b (sometimes also phase 1a and phase 1b). While this makes a lot of sense from the operational and risk-reducing view, we also want and need to model this in our financial models. But what are the probabilities for phase 2a and phase 2b? Typi-

cally, only transition probabilities for phase 2 are known. This is very inconvenient.

How to split phase 2 success rates?

There is almost no data available on phase 2a and 2b transition probabilities. We are only aware of one publication from Recombinant Capital, stating phase 2a probability as 77% and phase 2b probability as 64%[1]. This would mean that the overall transition probability for phase 2 were 77%*64%=49%. Of course, this might be true for the sample used for that publication, but in general phase 2 transition probabilities might well be different (mostly lower). However, that data contains some valuable information, namely that phase 2a is easier to pass than phase 2b; which is easily explainable with the different goals of the studies (dose finding vs. efficacy). Ideally, we take a phase 2 transition probability and split it in a probability for phase 2a and phase 2b such that, first, the product of the two probabilities matches the overall transition probability for phase 2, and second, that the weights between phase 2a and phase 2b correspond to the above two probabilities. If the probabilities were exactly the same, then they would simply be the square root of the phase 2 probability. But as the data suggests, we have to tweak them a bit in favour of the phase 2a probability. This can be done using the formulae as displayed in table 1.

Table 1: Phase 2a and 2b transition probabiities.

Phase	Transition probability
Phase 2	p_2
Phase 2a	$p_{2a} = p_2^{\left(\frac{\ln(77\%)}{\ln(77\%)+\ln(64\%)}\right)}$
Phase 2b	$p_{2a} = p_2^{\left(\frac{\ln(64\%)}{\ln(77\%)+\ln(64\%)}\right)}$

Success rates for phase 1/2a or 2b/3 trials

What probabilities should we use for other trial designs that seemingly skip the one or the other step in the common phase 1-2-3 paradigm? Of course, a drug will only get approved if it fulfils the necessary conditions with respect to safety and efficacy. The overall success rates are not impacted by the trial designs. At one point or the other you will find out whether the drug is efficacious or safe. So the product of the probabilities for the trials of the drug should match the product of the phase 1, 2, and 3 probabilities. A phase 1/2a takes the drug to the stage after a phase 2a trial. So the probability should be the product of the transition probabilities for phase 1 and phase 2b. For a phase 2b/3 the probability would be likewise the product of the transition probabilities of phase 2b and phase 3. Meanwhile we also see phase 1a and 1b trials. We are not aware of any data telling us something about the split of the phase 1 probabilities, but a similar approach like for phase 2a/b could be applied.

[1] Piercey, Lisa, „Phase 2 Clinical Trials: The New Emphasis in ‚Go/No Go' Decisions?", Signals Magazine, Recombinant Capital, 2004.