How to become a maker of tomorrow’s medicines using Real Options Theory

Paul Janssen Futurelab Leiden offers a new international blended education & training program for talented biomedical scientists on the development of novel medical interventions using the Real Options Theory. The aim is that these future chief scientific officers will change the entire drug development process.

Bedaquiline is a highly effective drug against a form of tuberculosis which is resistant to all other antibiotics. Patients in developing countries are clamoring for it. In an Indian court this month, a father won the right to have the expensive drug reimbursed for his daughter and similar patients. If other countries follow suit, bedaquiline will be a monster hit.

Curiously enough, bedaquiline was a whisker away from never making it onto the market. During its clinical development, the management of the company Janssen Pharmaceutica terminated the project. The discovery scientist, however, managed to convince his bosses that there was a future for the drug and he was allowed to conduct one more clinical trial – which turned out really well.

More information on Paul Janssen Futurelab’s education & training program can be found at www.PaulJanssenFuturelab.eu
The case of bedaquiline shows how small the difference is between success and failure in the billion-euro business of drug development. From one moment to the next, any project can go from being the next cash cow to being the next white elephant. Researchers at pharmaceutical companies therefore need to be able to stand up to the people holding the purse strings.

In order to arm those scientists, Paul Janssen Futurelab, a new initiative of Leiden University Medical Center in the Netherlands, is launching a new international education and training program. The program, supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw), is the first of its kind. “The course is designed for graduated biomedical scientists who are already in work”, says director Marcel Kenter. “It is aimed at specialists who wish to broaden their knowledge, take the next step in their careers and possibly move up to become CSOs.” CSO is the abbreviation of chief scientific officer, the person responsible for science policy at a pharmaceutical company. At small biomedical start-ups, the CSO is often also the founder, the inventor seeking to turn his idea into a reality. In large companies, the CSO usually sits on the board with the Chief Financial Officer (CFO) and the Chief Executive Officer (CEO). “In that role, you oversee the entire process of drug development – from initial idea to the market – with a scientist’s eye,” says Kenter.

"Making medicines the way energy companies exploit oil fields"

Participants of the blended (online + on-campus) education program learn about the process of drug development with the help of case studies from the business world, such as that of bedaquiline. “Real-life stories about breakthroughs, successes but also stories about costly failures, boardroom fights, directors quitting and companies going bankrupt,” says Kenter. “We give them anonymized teaching cases and they have to work on assignments based on those cases with fellow-participants. Afterwards, we present what really happened.”

Slick movie

The learners of the online course are also shown lots of video clips, in which thorny issues are discussed. The main feature is a slick Netflix-like drama series for which professional actors and a film crew were hired. In it, a young scientist succeeds in bending a research project to her will through perseverance, hard work and using the Real Options Approach.

Claire is a brilliant young neurologist who has just finished her PhD project and has switched from a university medical center to a biotech company. The company is developing a compound ITL4037, for the treatment of a neurological disorder. She is astonished at what she sees of the standard development process, and in particular the fact that the effectiveness of the drug is not evaluated at the start of the clinical development program. As a scientist, she is keen to know if it will cross the blood-brain barrier sufficiently to be effective. “Can’t we test for that now?”, she asks. “No”, says her boss Peter, who has already developed numerous products himself: “That would be extremely expensive.” Too expensive, apparently.

What Claire proposes is nothing less than a revolution. The pharmaceutical industry is organized around a linear development procedure in which, following animal study, a drug is first tested for safety in healthy volunteers (phase I), before the optimum dose and effectiveness are tested in clinical trials on patients (phases II and III respectively). The accounting models assume that the big money will be spent on the phase III clinical trials with patients.
Claire’s idea, which proposes spending more research money at an earlier stage, doesn’t fit that model.

“The whole project would be extended by at least six months, while the required research material would cost a few million extra”, explains Kenter. “The accountant would say: “Your proposal would diminish the Net Present Value of my entire development project.” The scientist would say: “If we spend a little more money now, we will know whether the drug is sufficiently effective at entering the brain. If not, we can halt the development program and we won’t need to conduct the most expensive part of the research. If it does, we can determine the optimum dose for the studies with patients (also using the animal data). That will also save us time and money later on.”

Oil fields
This methodology is familiar from the oil industry. When an oil field is discovered, oil companies wrestle with questions like: how much oil does it contain, how easy will it be to extract and how high will the oil price be when the oil comes out of the ground in about 10 years’ time? These uncertainties are all entered into a complex calculation model which oil companies help to decide whether to invest and exploit an oil field or not.

Kenter et al. are teaching their learners this decision model which is based on the Real Options Theory. “We have modified the model slightly and altered it so that it helps the scientists to identify the most efficient development route. It shows which scientific questions need to be answered first in the development program, even if this result in higher costs initially.”

In this way, Paul Janssen Futurelab hopes to put an end to the idea that the regulatory body European Medicines Agency (EMA) only approves drugs if they have been researched according to the standard linear phase I - phase II - phase III pathway. Kenter: “Many drug developers believe this, but it isn’t true. For this reason, in the online course we have an interview with the senior medical officer of the EMA, who says: ‘Regulations have to follow science, science doesn’t have to follow regulations’. In oncology, deviating from the standard development pathway is already known, but it needs to become more common.”

Claire gets five minutes to put her case to Head of Research Peter and CEO Frank, and she once again asks to be allowed to do the trial. She opens Futurelab’s online tool and asks them for a few details, such as the estimated total development costs and the key scientific questions to be answered in the development program. Once all the parameters have been entered, the tool produces the most optimal development route showing that also for financial reasons it makes sense to perform her trial early on.

There is plenty that can go wrong in clinical trials. Take the fatalities during the trial on probiotics in the Netherlands. Cases like these are also covered in the education program says Kenter, who has himself published on the failed trial on the antibody TGN1412 (Lancet 2006, BJCP 2015). In 2006, an experimental drug against an autoimmune disease was tested on six healthy young men in London. They became critically ill and eventually one of them lost finger tips, toes and a foot. The drug had first been tested on Cynomolgus monkeys without a problem, and was given to the healthy volunteers in a dose that was 500 times lower. Still the research subjects suffered from severe adverse effects. Apparently something was terribly wrong. “Crucial scientific questions were not answered beforehand. Afterwards it became clear that the starting dose was still much too high”, says Kenter. The biotech company went bust, a Russian firm bought the patent and successfully re-tested TGN1412 – at a much lower dose still. Kenter: “It is striking how little we learn from mistakes made. In our education and training program, we aim to do just that.”