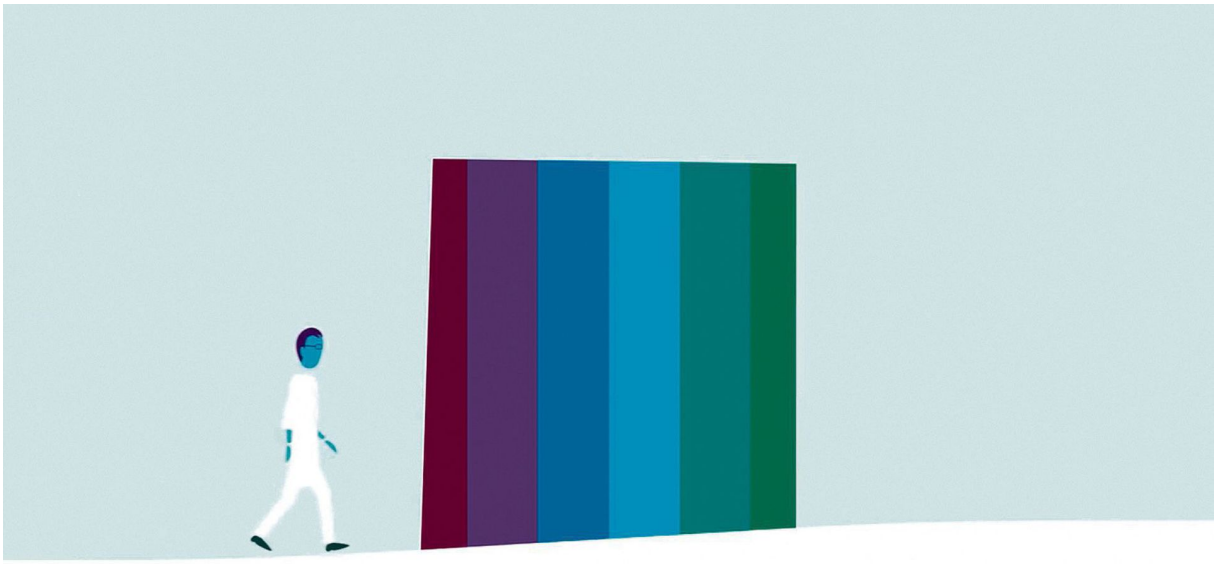
Karel Berkhout, NRC Handelsblad , 27 January 2017

How to become a maker of tomorrow's medicines

Biomedical scientists can now come to Leiden to be prepared for the pharmaceutical industry. 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 development, the management of manufacturer Janssen Farmaceutica nearly pulled the plug because it was thought the side effects could result in compensation claims. The discovery scientist, however, managed to convince his bosses that the side effects were manageable and he was allowed to conduct one more clinical trial – which turned out really well.

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 study 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 part of Leiden University Medical Center, is launching a master's degree. The education 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 graduate 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.

"Researchers should make medicines the way energy companies exploit oil fields"

Participants 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 boardroom fights, directors quitting and companies going bankrupt," says Kenter. "We give them anonymized cases like these and they have to work on assignments based on those cases with fellow-participants. Afterwards, we show them how things turned out in reality."

Slick movie

The leaners are also shown lots of (online) clips, in which thorny issues are discussed. The main feature is a slick half-hour movie 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 and hard work.

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 study. 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 development procedure in which, following animal study, a drug is first tested for safety in healthy volunteers (phase 1), before the optimum dose and effectiveness are tested in clinical trials on patients (phases 2 and 3). The accounting models assume that the big money will be spent on the clinical trials with patients.

Claire's idea, which proposes spending a lot of 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: this test would diminish the value of my entire 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 program and we won't need

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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 use to decide whether to exploit an oil field or not.

Kenter et al. are teaching their learners this model, the real options theory. "We have simplified the model slightly and altered it so that it identifies the most efficient development route. It shows which scientific questions need to be answered first, 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 EMA only approves drugs if they have been researched according to the standard method. Kenter: "Many drug developers believe this, but it isn't true. For this reason, in the film 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 procedure 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 study. She opens the online tool and asks them for a few details, for example about the patients. Once all the parameters have been entered, the tool produces the result that also for financial reasons it makes sense to perform her study early on.

There is plenty that can go wrong in clinical trials at a later stage. Take the fatalities during the trial on probiotics in the Netherlands. Cases like these are also covered in the study program says Kenter, who has himself published[1] 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 lost finger tips, toes and a foot. The drug had first been tested on Cynomolgus monkeys without a problem, and was given to the research subjects in a dose that was 500 times lower. "Crucial scientific questions were not answered beforehand. Afterwards it became clear that the 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 study program, we aim to do just that."

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4386939/

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