The past, present and future of medicines development

Some pharmaceutical industry analysts believe that the present medicines development model has come to a dead end. Scientific progress can materially alter the course of medicines development. The objective is to increase the probability of success, to shorten the time from development to market, and to reduce costs. This would enable the development of new medicines in the future.

The drug development process from initial testing to marketing authorisation usually takes about 10 years and costs hundreds of millions of euros. In the past few decades, the costs for one successful development process have grown tenfold while the number of new medicinal substances per year granted marketing authorisation has remained unchanged. No wonder many feel that the present development model is unsustainable and in need of modification.

An analysis, provocatively entitled 'Exit Research – Create Value', was commissioned by investment bankers and published a few years ago, and sent a very clear message to the pharmaceutical industry (Baum et al. 2010). Personally, I am more optimistic, and believe that more predictive models, new technologies and more efficient use of resources will improve the situation.

The discovery of a new medicine: the traditional model

Medicine development begins with the hypothesis that the deceleration or acceleration of a protein in the human body (target) will commence a biological chain of events that will affect the course of the disease being studied (figure 1). The initial study makes use of tool molecules, and if the findings support the hypothesis, the actual drug discovery project begins.

Computer modelling (in silico) of the molecules allows scientists to investigate how these bind with the target protein. Suitable molecules are synthesised in the laboratory to produce the appropriate chemical compounds, in the hope that they contain compounds that affect the target protein (hits). From these, a few lead molecules, or leads, undergo further lead optimisation with the objective of selecting the final candidate for further studies. Selection is based on the efficacy of the studied molecules in the modelled diseases, and on their safety, absorption, distribution, metabolism and excretion (ADME).

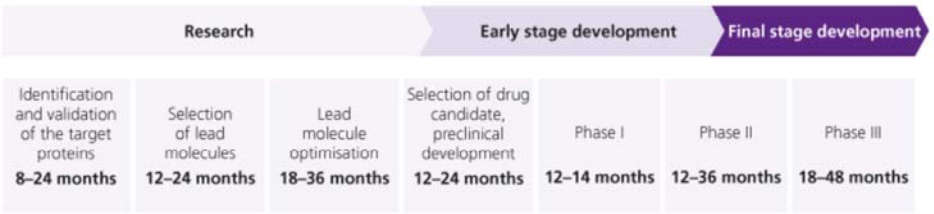
Final drug candidates will undergo safety tests. If no problems arise, the molecule will be used for clinical development. Simple drug formulations are used in the preclinical trials. These are developed during the clinical trial stage with the objective of completing the final formula before the Phase III trials that precede marketing authorisation.

Clinical trials are divided into four phases. Phases I, II and III precede the marketing authorisation, while Phase IV trials are conducted after the marketing authorisation has been granted. In most cases, healthy volunteers are recruited to Phase I trials, if the characteristics of the medicinal substance permit. The purpose of Phase II trials is to prove the efficacy of the drug for the first time in patients, and to establish the optimal dose for further trials by balancing adverse reactions and efficacy. The findings are finally confirmed in the Phase III trials, usually in two studies and sometimes involving thousands of patients. These studies provide the clinical foundation for the marketing authorisation application.

As they lead to marketing authorisation the studies are aiming to validate the hypothesis, which is why the number of variables is kept low and there are several exclusion criteria. Although scientifically valid, this principle affects the research results, which fail to provide a full picture of real-life patients. Consequently, the objective of Phase IV trials (real life studies) is to establish which patients benefit most from the drug and why.

The process generally takes more than 5 years to reach the real-life stage, with a success rate of only a few per cent. The rate rises to 10–20% after the efficacy of the medicinal substance in humans has been proven for the first time. Only about half of Phase III trials lead to marketing authorisation. The process clearly needs a major shake-up!

Figure 1. Stages of the traditional medicines development model.



A shared risk is easier to bear

Drug research today is based on constantly expanding collaboration. For instance, the objective of the Innovative Medicines Initiative, a joint undertaking between the European Union and the pharmaceutical industry association EFPIA, is to support collaborative research projects conducted by industrial and academic experts in order to solve problems in medicines development (www.imi.europa.eu).

To share the risks involved, pharmaceutical companies build collaborative networks within the industry and with universities and small companies. Although identification of new target proteins is largely the responsibility of universities, pharmaceutical companies become involved at the validation stage. In fact this is necessary as only 10–25% of target validations carried out by universities can be repeated in industrial settings (Prinz et al. 2011, Begley and Ellis 2012).

Generally speaking, use of all available competence and knowledge worldwide is urged whenever research involves high risks. And even then, only the very best succeed.

Room for improvement in the predictability of preclinical trials

Translational medicine is a discipline within research that aims to bridge the gap between preclinical findings and clinical medicine. There are several ways to improve the predictability of preclinical drug trials.

The biggest problem in the pharmaceutical industry is that projects halt at Phase II due either to lack of efficacy or adverse reactions. The successful project is founded on correct selection of all variables: target protein, medicinal substance, dose, and patient. In the constantly evolving field of systems pharmacology, attempts are being made to create mathematical models and simulations for drug dynamics in the

biological chain of events associated with a disease (Vicini and van der Graaf, 2013). Success requires not only systems biology but physiologically based pharmacokinetics (PBPK): in other words, an understanding of how drugs act in various organs, and with what consequences. We have seen indications of systems pharmacology increasing preclinical translation and helping to discover the right prodrug for each target protein, while also providing a general idea of the dose.

Induced pluripotent stem cells (iPS) could be used more extensively to predict safety (Weltner et al. 2014). The greatest prospect is probably that these cells would source the development of treatments for degenerative diseases. Long before that, however, these cells enable the investigation of tissue-specific adverse reactions. For example, human peripheral neurons grown in stem cells from fibrocytes can be used to study the risk of neuropathy associated with a particular drug. At some point, we expect the first studies on the efficacy of a drug in humans will be conducted in vitro.

I have personal experience of failed Phase III trials where, when contemplating the reasons for failure, we doubted whether the drug had ever reached the site of action in humans. A drug is only effective if it reaches the target tissue and binds with the target protein, resulting in the required pharmacological effects. This so-called three-pillar model, originally introduced by Pfizer, represents an area of systems pharmacology and offers an example of how direct lines can be drawn between pharmacokinetics and pharmacodynamics (Vicini and van der Graaf 2013).

Advances in clinical research

Preclinical research is making giant leaps in order to improve the productivity of drug research. Once a new drug candidate has been selected for clinical trial, the selection is final and the molecule itself can no longer be modified. Nonetheless, there is still scope for development in clinical research.

A poorly conducted study can result in the rejection of a good molecule, or give false hope regarding a molecule that will fail later. If the drug development process for a molecule fails it should do so as early as possible, in the preclinical stage, or no later than in the first proof-of-concept studies: in other words, before the close of exploratory development. Final studies conducted in the clinical development process are called confirmatory development; these involve establishing the correct dose and repeating it in a large number of patients.

Once the right target and the right molecule are discovered in preclinical trials, the objective of clinical trials is to establish the correct dose and identify the right patients. Finding the right dose can be made more effective through adaptive design.

An adaptive clinical trial involves changing the study design on the basis of research data accumulated, while nonetheless maintaining the validity and integrity of the results. This allows the merger of certain elements, such as Phase IIb and III trials, into a single trial. Various dose levels are studied at the beginning of the trial, and one or two best doses are selected in accordance with predefined criteria for Phase II without needing to suspend the trial or compromising blinding. As a result, we can accelerate clinical research, lower the costs, and reduce patient exposure to placebo treatment or to risks of administering doses of experimental drugs that are too low or excessive (Orloff and Stanski 2011). An adaptive approach will soon be introduced in the marketing authorisation procedures for medicines, allowing patients to obtain limited access to innovative medicines sooner.

Although medicines already improve health and save lives, there are still regrettably many patients whose response to treatment is inadequate or who suffer from adverse drug reactions. If we were more often able to identify the right patient for a particular drug, fewer patients would be required for clinical trials, resulting in lower costs. One possible solution is the personalised drug, with patients being selected on the basis of their biomarkers. This is already the case with many cancer therapies.

Therapeutic value of drugs to be assessed with consistent criteria

Once a drug has been registered, price and reimbursement applications should indicate not only efficacy and safety but the value of the drug to society and to the patient. Patient-related outcomes and cost-benefit analyses will become increasingly important. As a doctor and a taxpayer, I'm pleased with this development.

Determining therapeutic value nonetheless presents certain problems. Before marketing authorisation is granted, medicines are assessed at the European level, but value determination following authorisation takes place at the state level (or even at regional level in some countries) in line with criteria that lack transparency and sometimes appear to be based solely on cost savings.

There is plenty of room for improvement in this area. It would be best to set common rules for the value of a drug, and insist on universal compliance. Criteria should emphasise the patient's best interest. Such improvement will not take place through any action by the pharmaceutical industry: what is needed is political will.

Medicines development requires knowledge, skill and a lot of luck

I hope the new trends in medicines development I have outlined here (figure 2) will reduce the role played by the luck element. Patients and society need new, innovative medicines. A slight increase in the probability of success would bring my dream job in drug research and development even closer to the ideal.

Figur 2. Läkemedelsutvecklingen i framtiden.

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LITERATURE

Baum A, et al. Exit Research – Create Value. Morgan Stanley Research Report 2010, pp. 1–55.

Begley G, Ellis L. Raise standards for preclinical drug research. Nature 2012; 483: 531–3.

Orloff F, Stanski D. Innovative approaches to clinical development and trial design. Ann Ist Super Sanita 2011; 47(1): 8–13.

Prinze F, et al. Believe or not – how much can we rely on published data on potential drug targets. Nat Rev Drug Discov 2011; 10: 712–3.

Vicini P, van der Graaf P. Systems pharmacology for drug discovery and development. Clin Pharmacol Ther 2013; 93: 379–81.

Weltner J, et al. Indusoidut pluripotentit kantasolut lääketieteellisessä tutkimuksessa. Duodecim 2014; 130: 785–92.