INNOVATION FOR TOMORROW'S MEDICINE

STRUCTURAL SOLUTIONS FOR A SYSTEM UNDER PRESSURE

TNO innovation for life

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Our growing understanding of pathological processes is enabling the development of drugs that are 'tailored' to specific patients or groups of patients, and hence far more effective. At the same time, developing tomorrow's medicine is prohibitively expensive, time-consuming and risky. New partnerships and technological developments to speed up the process are possible – and indeed vitally important – to cut costs and stimulate the development of these drugs so that they can be made available to patients sooner.

THE PROBLEM IN FIGURES

The journey of a potential drug from laboratory to patient currently takes some thirteen years. The likelihood of it failing during expensive clinical trials is around 90 percent[1] due to lack of efficacy (60 percent) and safety considerations, i.e. the fact that the final product has harmful side effects in humans (40 percent). The cost of developing a new drug nowadays is estimated at between 1.3[2] and 2.5[3] billion euros. The high failure probability and costs make the risks to the industry very high, causing the prices of drug to rise and the pressure on healthcare spending to simply become too high.

STRUCTURAL SOLUTIONS

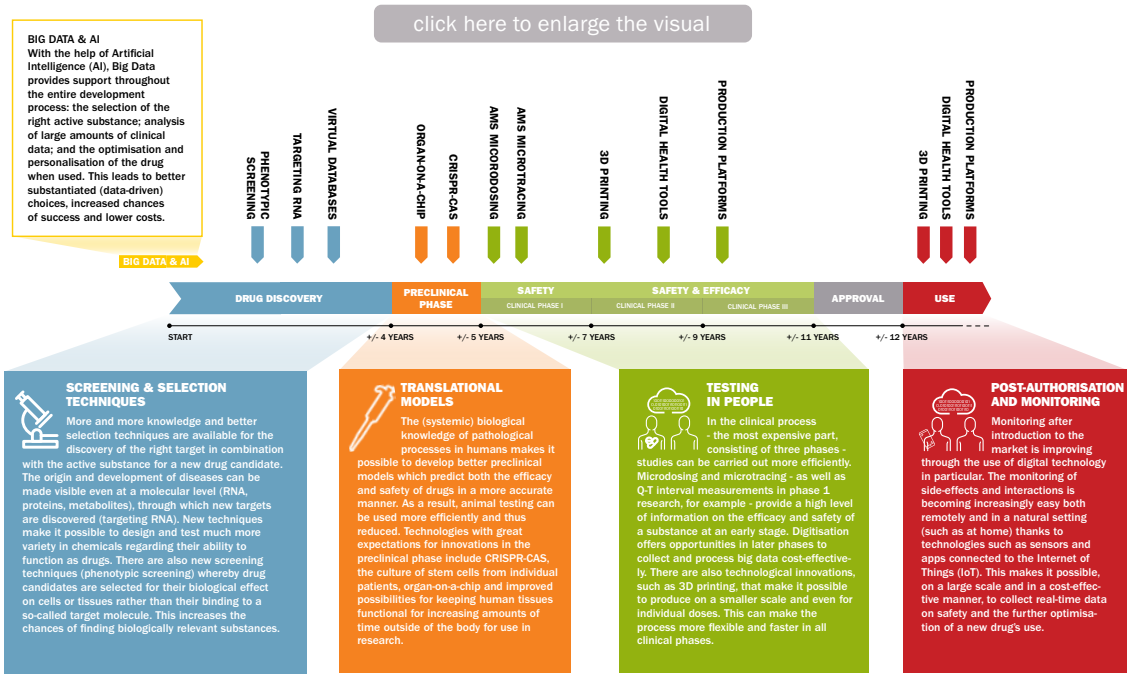
TNO is working hard to find innovations that will enable tomorrow's medicines to be developed cost-effectively. The answer lies in technology to speed up the process, as developing drugs faster saves costs and means that they are available sooner. And that's not all: technology also enables us to focus on an increasing amount of research with human tissue and organs in the preclinical phase, or even to skip parts of preclinical research and carry out direct research in humans. As a result, research can be accelerated and fewer laboratory animals need to be used.

This document outlines some technological advances in drug development, followed by an example of a technology that is proven to speed up the drug development process. We conclude by calling upon the public and private sectors to coordinate their efforts to implement efficient innovations.

1 De ArgumentenFabriek, 'Zó werkt de geneesmiddelenzorg' (Nov. 2019)
2 De Tijd: 'Kostprijs nieuw medicijn lager dan gedacht' (Mar. 2020)
3 Gupta Strategists report 'The cost of opportunity – A study on pharmaceutical R&D costs' (2019)

TRENDS IN DRUG RESEARCH

Many technologies are being developed that could contribute to the development or production of tomorrow's drugs. The figure below shows a selection of these promising technological advances.



VISUALISATION

Examples of technological trends aimed at speeding up the process of drug development

For an enlargement of the visualisation, see page 9

Many of these technologies are designed to gather more information on the biological properties of a drug candidate at an earlier stage of the development process (front-loading), thus reducing the risk of failure at a later stage (early de-risking). This is based on the fail-fast principle: if a drug has a high failure probability, it is better to find this out quickly and halt its development process before too much time and money has been spent.

COHESIVE DEVELOPMENT

Many of these advances are typically highly fragmented. At present, parties often work on partial solutions with no integrated approach to systematically accelerating the process of drug development. In addition, most of the research budgets are spent on finding new and better drug candidates. This is important but does not contribute significantly to the generic acceleration of the development of drugs. In fact, the complexity of new drug candidates often makes the development task even more onerous. In addition to developing new drug candidates, it is all the more important to focus in particular on technologies that speed up the development process, as this produces both financial gains and potential savings. A drug that comes onto the market sooner will be available to patients sooner. Also, the longer the remaining patent life, the better chance the manufacturer has of recovering its investment. The average annual turnover of the top ten drugs in 2018 was over 7 billion euros, so coming onto the market one or two years earlier can make for a revenue difference of billions of euros. In other words, it produces enormous financial gains that stand to benefit the industry, government and patients alike.

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MICROTRACING: AN EXAMPLE OF PROVEN PROCESS ACCELERATION

New drug candidates need to be tested for efficacy and safety. In order to guarantee safety, the regulatory authorities demand that research be carried out to establish whether the drug is converted into (potentially toxic) breakdown substances in humans, known as metabolites. This research involves first administering a radioactive form of the drug, a tracer, to various species of laboratory animals to track down any (unrecognised) metabolites. The same drug tracer is then administered to healthy volunteers, and the researchers check whether the metabolites that develop in humans were also found in the laboratory animals. If not, the possibility of a unique human metabolite that proves toxic in humans cannot be ruled out. Given the high dose of radiation required for this kind of research, it is only ethically acceptable for healthy volunteers if the drug has been shown to be effective. This research therefore takes place during the later stages of the clinical trial, some of it during the final and most expensive of the three clinical phases of drug development.

TNO has developed a unique technology to speed up the process: microtracing combined with Accelerator Mass Spectrometry (AMS), including fully automated sample preparation and analysis. Microtracers are forms of the drug that contain an extremely low dose of the radioactive material. The very low radioactivity removes the ethical problems, and these tests can be carried out during the first clinical phase instead of the final, most expensive phase of clinical research. It does not cause delays;[4] on the contrary, research with AMS can concretely shorten the development process of new drugs by approximately two years (early de-risking).

Unique TNO research using AMS can concretely shorten the development process for new drugs by approximately two years.

4 Drug Discov Today. 2016 Jun; 21(6):873-9. doi:10.1016/j.drudis.2016.03.012. Epub 2016 Mar 29. The impact of early human data on clinical development: there is time to win.

If microtracing studies reveal the presence of large quantities of dangerous metabolites, this may stop the further development of these drugs. As microtracing studies can be carried out at an early clinical stage, expensive clinical studies can be avoided (fail fast). Also, early information on the metabolism of a drug in humans can be used to make animal studies more efficient and reduce the need for them. This approach reveals the human metabolism sooner, so no radioactive metabolism studies in animals are needed. The number of laboratory animals normally used for this type of metabolite research can thus be reduced to zero. Having developed fully automated sample preparation, TNO is the only organisation in the world that is able to use this AMS technology for drug development as a matter of routine. The applicability and validity of this method have been proven on several occasions in collaboration with pharmaceutical partners. We would like to emphasise that TNO was able to develop this technology with the aid of Dutch government funding.

HOW DOES AMS WORK?

The technical mechanism of AMS is as follows: the drug is labelled with carbon-14 atoms and then administered in extremely small quantities to patients and/or volunteers in the clinical phase of drug development. Blood, plasma, urine or feces sampes are taken from them at various times. The samples are classified in terms of various molecules using Ultra-Performance Liquid Chromatography and then burnt using an Elemental Analyser, producing CO2. The number of carbon atoms is then measured. Those atoms are ionised in the AMS system by bombarding the CO2 molecules with the alkali metal caesium, causing them to disintegrate into atoms. At the same time, the carbon atoms take on a negative charge. The mix of charged carbon atoms is separated using a magnet and accelerated, enabling the C14 ions to be separated from the other carbon ions. Each C14 isotope is counted and the C14/C12 ratio is calculated. The ratio and the total amount of carbon can be used to calculate how much drug material is found in each specific fraction of the sample. This information enables the determination of the amounts of specific metabolites of the drug candidate that are formed in the human body. As a result, the pharmacokinetic properties (how the drug is distributed throughout the body) and the metabolite profile data for drug candidates are available before large-scale preclinical and clinical trials start.

APPEAL FOR A COORDINATED APPROACH

The world of drug development is characterised by conflicting interests, emotions and market forces. The focus ought to be on patients, but this is not always the case. It is a challenge for both the public and private sectors to guarantee the development of innovative, accessible and affordable drugs, not only now but in the long term. The development and use of technology plays a vital role here, and a dialogue between the stakeholders is in the interests of society.

BOTTLENECKS AND INVESTMENTS

Both public and private sectors are investing in innovative technology, but they are not coordinating their investments and development efforts enough yet. A dialogue between the public and private sectors is needed to gain a clear idea of where investments and innovations are required. We need to find out precisely where in the process the bottlenecks lie that are increasing the costs and where there are opportunities for acceleration. Both the industry and government stand to benefit from this. It will enable the government to target investment at relevant process innovations, which – financed partly from public funds – can (sometimes substantially) reduce the major risk to manufacturers - as the use of AMS has proven, for instance. Public money should be used to improve processes, which then need to be accepted by the regulators. Greater government involvement in this process will raise the need for amendments in the rules and regulations and thus bring them about sooner. The Ministry of Health, Welfare and Sport could decide to take this investment into account in discussions with pharmaceutical companies on drug prices. As a result, lower development costs would benefit not only the shareholders of the pharmaceutical companies but also the public at large.

ACHIEVING PROGRESS BY JOINING FORCES

Now that the European Medicines Agency (EMA)[5] has been relocated to the Netherlands, giving a gigantic boost to the Dutch Life Sciences & Health (LSH) ecosystem, this is a good time to pull out all the stops. Several organisations and initiatives on the part of the various stakeholders have already opened up opportunities for a dialogue. The organisation Fair Medicine[6] has come up with a new way of working together to provide everyone with access to safe, effective and affordable drugs. The government has launched the Action Programme 'New opportunities for Top Sector Life Sciences & Health', which focuses on national coordination, strategic acquisition and affordable new treatments. Part of this is the FAST (Future Affordable and Sustainable Therapy)[7] programme, which can serve as a national platform.

5 https://www.ema.europa.eu/en
6 ttps://www.fairmedicine.eu/en/our-approach/how-does-fair-medicine-work/
7 https://www.zonmw.nl/nl/onderzoek-resultaten/translationeel-onderzoek/future-affordable-and-sustainable-therapies/programma-detail/goed-gebruik-geneesmiddelen/

These programmes and initiatives give stakeholders opportunities to join forces and represent their interests. TNO supports these initiatives and is making its knowledge of technology and innovation processes, its facilities and its organisational strength available to develop and implement usable process innovations which stand to benefit those stakeholders. It is very important, however, for the major companies that develop and market drugs to be involved as well – in particular, the divisions involved in new drug research and development, as these will be the first to incorporate innovative technologies into their internal development strategy.

Together, we can develop drugs that are better tailored to the needs of patients, that become available sooner and that cut the cost of development.

INNOVATIONS FOR TOMORROW'S MEDICINE

This document is a call for a coordinated approach. Existing initiatives are a first step in that direction, but they are still fragmented. What is needed is an initiative in which all the stakeholders are represented, as public authorities and large and small companies will need to invest jointly in the development process of tomorrow's drugs.

The development of the AMS technology has proven that the gap can be bridged and that government investment can speed up processes in companies. TNO is accustomed to working with small and large pharmaceutical companies on a project basis and has implemented innovative technological concepts through its contacts with (inter)national companies and public authorities. TNO is partly funded by public sources, but its research is independent. In a word, TNO speaks the language of business and government and works in the interests of society at all times.

These characteristics make TNO the ideal party to concretely help bridge the gap between the public and private sectors in order to develop technologies that make this acceleration possible, to open the regulatory doors to this innovation and to allow industry to apply this technology directly in the development process.

TNO is keen to use its experience in a broad, coordinated approach so that the technological possibilities are optimally used to further improve the drug development process. In this way, we can meet the challenges posed by 'tomorrow's medicine' in the interests of the patient.

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BIG DATA & AI
With the help of Artificial Intelligence (AI), Big Data provides support throughout the entire development process: the selection of the right active substance; analysis of large amounts of clinical data; and the optimisation and personalisation of the drug when used. This leads to better substantiated (data-driven) choices, increased chances of success and lower costs.

SCREENING & SELECTION TECHNIQUES

More and more knowledge and better selection techniques are available for the discovery of the right target in combination with the active substance for a new drug candidate. The origin and development of diseases can be made visible even at a molecular level (RNA, proteins, metabolites), through which new targets are discovered (targeting RNA). New techniques make it possible to design and test much more variety in chemicals regarding their ability to function as drugs. There are also new screening techniques (phenotypic screening) whereby drug candidates are selected for their biological effect on cells or tissues rather than their binding to a so-called target molecule. This increases the chances of finding biologically relevant substances.

TRANSLATIONAL MODELS

The (systemic) biological knowledge of pathological processes in humans makes it possible to develop better preclinical models which predict both the efficacy and safety of drugs in a more accurate manner. As a result, animal testing can be used more efficiently and thus reduced. Technologies with great expectations for innovations in the preclinical phase include CRISPR-CAS, the culture of stem cells from individual patients, organ-on-a-chip and improved possibilities for keeping human tissues functional for increasing amounts of time outside of the body for use in research.

TESTING IN PEOPLE

In the clinical process - the most expensive part, consisting of three phases - studies can be carried out more efficiently. Microdosing and microtracing - as well as Q-T interval measurements in phase 1 research, for example - provide a high level of information on the efficacy and safety of a substance at an early stage. Digitisation offers opportunities in later phases to collect and process big data cost-effectively. There are also technological innovations, such as 3D printing, that make it possible to produce on a smaller scale and even for individual doses. This can make the process more flexible and faster in all clinical phases.

POST-AUTHORISATION AND MONITORING

Monitoring after introduction to the market is improving through the use of digital technology in particular. The monitoring of side-effects and interactions is becoming increasingly easy both remotely and in a natural setting (such as at home) thanks to technologies such as sensors and apps connected to the Internet of Things (IoT). This makes it possible, on a large scale and in a cost-effective manner, to collect real-time data on safety and the further optimisation of a new drug's use.

VISUALISATION

Examples of technological trends aimed at speeding up the process of drug development

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