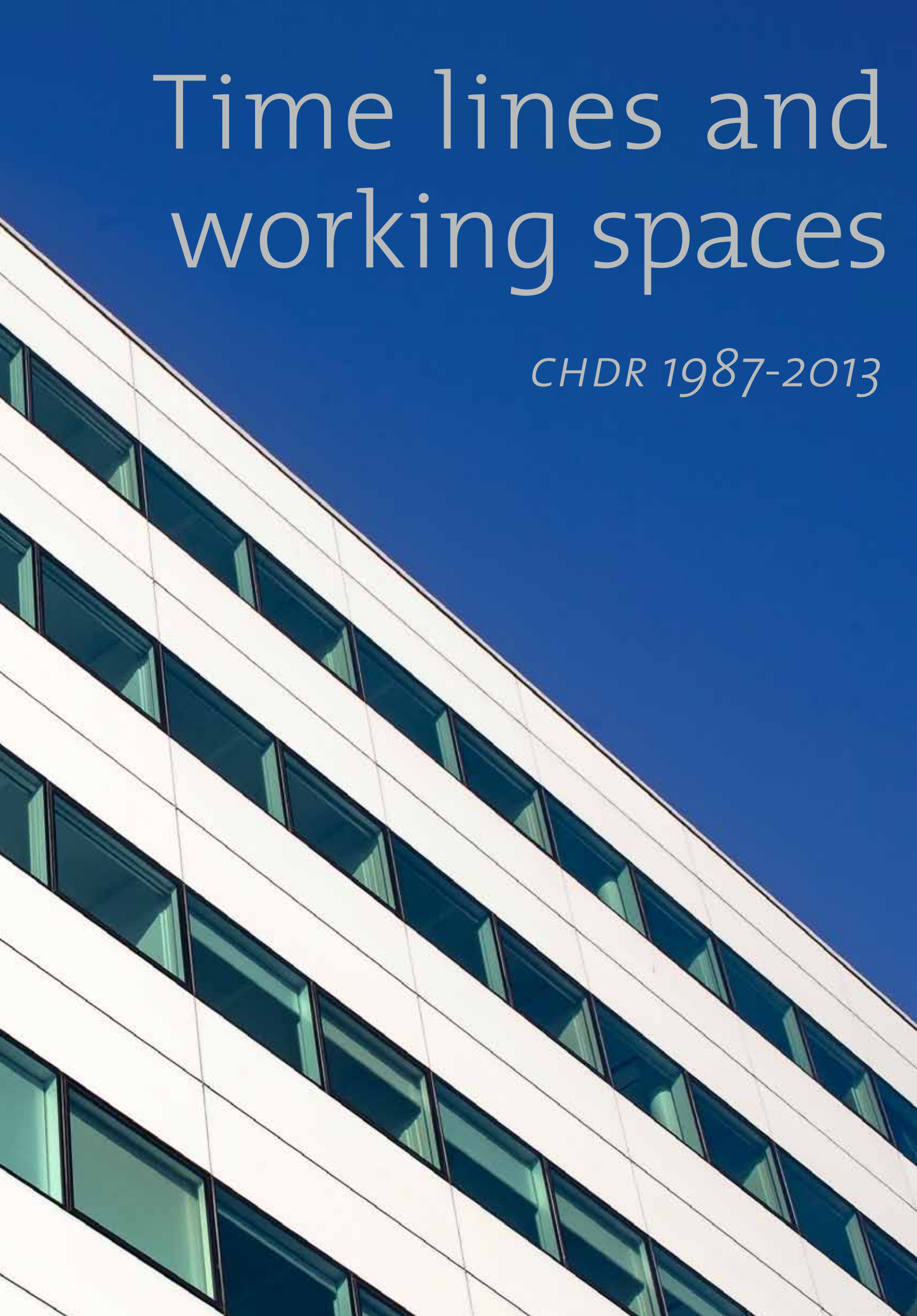
Time lines and working spaces

CHDR 1987-2013



Time lines and working spaces

CHDR 1987-2013

Dinosaurs, shared value and long timelines

The contents of this book may initially baffle the reader. Dinosaurs? Shared value? Why on earth would a simple research unit for phase I research want to write about paleontology or a new concept for capitalism introduced by a management guru?

First, let's be clear about one thing. CHDR is about research on prototypical potential new medicines in humans, nothing more and nothing less. However, this simple fact cannot be approached without a broader, long-term vision.
The organisation has its roots in the vision of Douwe Breimer who had the revolutionary idea to set up a drug research unit in Leiden. It grew from three people in a temporary prefabricated building in 1986 to 150 in the current world-class facility.

So, a long view of our world is required, both to make sense of the past and to plan the future. This is why CHDR has a Dinosaur Conference every 5 years, and in this book we present the motivation and proceedings of the first conference in 1997. The dinosaur reminds us that growing to a certain size is only possible when the world around you allows it. Giants in drug research like Paul Janssen and Nobel laureate Jim Black say things that are still relevant today.

The long view of CHDR is also reflected in our history, and this book contains stories about some of the long timelines (albeit not on a geological scale) that we value. The development of the NeuroCart over 40 years and the biomarker research at CHDR are stories that share a continuity of relations between people, as we continue to change and adapt each time the world changes. This is also true regarding our activities in education, which have resulted in one of the most frequently used and downloaded pieces of educational software in pharmacology.

Our values are long-term, and the result is perhaps best reflected in the concept of shared value that was proposed by Michael Porter from Harvard Business School. This is why we embrace this concept in our 25th anniversary symposium.

Long lines require people who are willing to stay the course, and in the book you will find many photographs of CHDR friends and employees, generally with a statement of where they ended up if they are not still at CHDR.

The world still needs many new drugs, and the era in which a single, dinosaur-like organisation can develop them single-handedly is over. The future is in lean and effective clusters of specialists that aggregate when needed; this is why we built the new unit as an open meeting place for such clusters. Our architects describe how they realised such a vision.

We hope you enjoy this festive publication, not only to see pictures of the past and what has happened in the last 25 years, but also to provoke some thoughts about how we should develop the medicines of the future. Paul Janssen, the founder of Janssen Phamaceutica, the predecessor of the JNJ subsidiary Janssen and one of the world's most famous drug developers (the company developed more than 70 drugs under his guidance) was one of the discussants at our first Dinosaur conference, and it is fitting to end this short introduction with a quote from one his publications from 1983:

> *'To make this great dream come true persistence is required, a faith in the dream. This is why superior drugs will only be found by inquisitive and candid researchers, living in a free world where ideals can still be realized and beautiful dreams can still come true. They will not be found nor even recognized by complacent, unimaginative and lazy-minded bureaucrats, soaked in regulations, old prejudices and habits of mind.'*

Thirty years later, this great man's vision is still an inspiration for many. We hope you will enjoy this book as a souvenir of your attendance at the opening of the new CHDR building. Even if you were not present, the fact that you have received this means we consider you a part of our group of longstanding friends. We hope that does not make you feel like a dinosaur, but if it does, this book should help you keep an eye out for what happens around you.

PART ONE

The CHDR dinosaur meetings

The series of CHDR 'Dinosaur' meetings, which take place every 5 years, started in 2002 when CHDR commemorated its 15th anniversary. The idea arose to have a small discussion meeting with both distinguished and young participants. The idea to host the meeting in the adjoining Museum of Natural History among the dinosaur skeletons (to be reminded what happened to an ecosystem when it did not watch the environment in which it operated) originated from Koos Burggraaf. We republish the palaeontological motivation, as well as the proceedings from the first meeting.

What football players and dinosaurs can teach us

The rise and fall of the dinosaurs is comparable to that of a multinational with a limited product line. A new invention, the egg, enabled the animals to move onto the land. Assorted new-fangled forms colonised various environments on earth. The Pterosaurs took to the air, the Ichthyosaurs and Plesiosaurs returned to the water, and the Dinosaurs settled the dry land. The latter group made use of another invention: walking on straight legs, which made them go faster and enabled them to travel greater distances. All sorts of new fashions developed, such as the strange horns on the heads of Hadrosaurs. An arms race between predators and prey resulted in animals such as *Tyrannosaurus rex*, whose huge teeth and bulk enabled it to hunt even large dinosaurs.

In the early days of the dinosaurs, when the continents were still joined and formed a single landmass, all dinosaurs were closely related. Once the continents started to drift apart, new and different forms of dinosaurs developed on the (now separated) continents. South America is a good example of this divergent development. The modified distribution of land and water masses resulted in a cooler climate. As a result, plant life also changed. Eventually, a meteorite struck the earth. The multinational Dinosaur could not cope with all of these changes. New inventions took over that were better adapted to the changed environment: birds and placental mammals, the former with the advantage of feathers, the latter of fur, and both warm-blooded. The multinational dinosaur was too highly specialised to respond adequately to the major upheaval that marked the end of the Cretaceous period. It collapsed and was succeeded by two new multinationals: birds and mammals.

(DIS)ADVANTAGES

Johan Cruijff, the Dutch soccer player, introduced a famous saying: 'Every disadvantage has its advantage'. This applies not only to football, but also to nature. The mammals and birds that lived in the shade of the dinosaurs turned a disadvantage (the meteorite impact) to their own advantage. Yet previously, the dinosaurs had also managed to turn a disadvantage into an advantage, and they subsequently piled success upon success. How exactly did this happen? The collection of Argentinean dinosaurs currently on display in Naturalis lets you follow the story of the dinosaurs, which evolved from tiny, agile omnivores into the largest and most fearsome predators ever.

Lagosuchus talempayensis, the oldest and most primitive creature displayed in the Dino Argentino exhibition, features a very successful innovation among lizards. The shape of the upper legs of *Lagosuchus* makes it possible to tuck the feet underneath its body rather than place them alongside its body. This adaptation offers a major advantage. Real lizards move their feet all the way along a half circle, but, balanced properly, *Lagosuchus* was able to support itself on one leg and swing the other leg forward in a straight line. Because the shortest distance between two points is a straight line, this ability gave *Lagosuchus* a minor advantage, as it was faster than other reptiles. We still classify the 30-cm-tall *Lagosucchus* as a reptile, but it was actually the first animal to exhibit the characteristic that made dinosaurs into dinosaurs: it held its body off the ground with its legs tucked underneath.

Although the new stance of the legs offered only a minor advantage, it opened the way to many new opportunities, which in the course of the following 150 million years led to a series of stunning successes. This group of animals with their feet directly underneath their bodies embarked on new developments when the pelvis evolved along two different trajectories: (1) in the Saurischians (reptile-hipped

dinosaurs), one of the three pelvic bones (the pubic shaft) pointed forward; while (2) in the Ornithischians (bird-hipped dinosaurs), the pubic shaft protruded both forward and also backward. Both types of pelvis permitted bipedal as well as quadrupedal locomotion.

ON TWO LEGS

Iachosucchus still moved about on all fours; however, an entire branch of the Saurischians started to walk on two legs: the Theropods. The Theropods' toes and fingers gradually disappeared, while their tails grew longer. Such a long tail might be viewed as cumbersome, as a long-tailed animal would be easier for a predator to catch. Yet again we observe the advantage of a disadvantage: the tail counterbalanced the front part of the body, moving the centre of gravity to a point above the hind legs. Thus, Theropods were enabled to become truly bipedal, and in turn were able to run much faster. The dinosaurs' neck adapted to their bipedal stance: the S shape of the neck allowed the animal to look forward! Bipedality originally offered the advantage of rapid escape (and therefore protection) from predators. The later bipedal dinosaurs grew extremely large and became predators themselves. The dentition of early bipedal dinosaurs was typical of omnivores, but real carnivore teeth evolved in later species. We have even come across double-hinged jaws, which enabled the owner to grab larger chunks of meat.

Eoraptor lunensis is one of these early bipedal dinosaurs. As evidency of omnivory, it had two different types of teeth: leaf-shaped teeth to eat plants; and sharp, curved teeth suitable for eating meat. *Eoraptor's* skeleton shows only a minor reduction of the fifth toe and comprises 40 tail vertebrae. In the *Herrerasaurus ischigualastianus* skeleton, the fifth toe has almost completely disappeared and the sharply recurved teeth and double-hinged jaws are signs of a real carnivore. *Herrerasaurus'* tail contained as many as 50 vertebrae.

At this point, we have only just arrived at the dawn of the dinosaurs: these fossils were found in Triassic deposits dating back some 200 million years. A little later, during the Jurassic period, this group evolved into the most dangerous carnivores ever: the Carnosaurs. A representative in the Argentinean collection is *Piatnitzkysaurus floresi*. His cousin 'Big Al', or rather the Allosaurus, is the cruel star of the movie Jurassic Park. Obviously, several adaptations were required for the brutes to grow this large. The pelvis had to bear a heavier, more solid body than that of earlier dinosaurs, which was achieved by the pelvis becoming attached to the spine by four vertebrae. Earlier dinosaurs only had three or even fewer vertebrae attached to the pelvis! To counterbalance the heavier, barrel-shaped body of this huge animal, the vertebrae were fortified by large spines. Similar to other predators, this beast also had large eyes so it could better see its prey. In Argentina, evolution continued along these lines until, during the Cretaceous period (100 to 70 million years ago), the most dangerous animal ever appeared in the Argentinean deposits: *Giganotosaurus carolinii*: a brute that beats *Tyrannosaurus rex* in size. We do not know much about this Giganotosaurus because only its skull has ever been found, but that skull is six feet long! Another interesting creature was *Carnotaurus sastrei*. This two-horned dinosaur, remains of which have been found in South America, underwent a distinctive evolution, as exemplified by the reduction of the front limbs. The conspicuous curvature of the humerus (upper-arm bone) and reduction of the ulna and radius in the lower front leg occurred very differently in *Carnotaurus sastrei* compared with its famous North-American counterpart. While T-rex had only two fingers left, Carnotaurus' hand still possessed four fingers. The two animals occupied the same niche on different continents and yet were not related. Clearly, rapid bipedal dinosaurs qualified for the niche of large predators; however, which family would become the apex predator on which continent apparently did not depend on the degree of reduction in front legs or fingers.

INTO THE AIR

Although the name suggests otherwise, birds evolved from the Saurischians (reptile-hipped dinosaurs), not from the Ornithischians (bird-hipped dinosaurs). The first birds were carnivorous and capable of rapid escape. Some scientists even assume that wings and feathers evolved as a kind of sieve to trap insects, when the animal spread its wings while it was running fast. Thus, a history of successful innovations in the Saurischians resulted in present-day birds: a group of animals whose evolutionary success continues to this day.

OTHER EVOLUTIONARY LINES

The Saurischians utilised many opportunities. In addition to the successful Theropodes, some representatives evolved in a completely different direction: they became quadrupedal. Evidence of the earliest known quadrupedal dinosaur, *Mussaurus patagonicus* (the mouse reptile from Patagonia), was found in Argentina and is at least 205 million years old. The *Mussaurus* specimen in Naturalis' exhibition is the youngest dinosaur specimen ever found. It is only a newly hatched baby, but its parents were quadrupeds that each grew to the size of a small pony. They lived in herds and were herbivorous.

In the wake of these early quadrupeds, many larger animals also arose in Argentina during the Jurassic period, 165 million years ago. One such example is the 10-metre-long *Patagosaurus fariasi*. Its pelvic girdle was attached to five vertebrae to support its heavy body. Just like present-day elephants, this creature walked on five toes with fortified metatarsals. This dinosaur also lived in herds and likely scraped the bark off of trees with its spoon-shaped teeth.

During the Jurassic and Cretaceous periods, the super-continent Pangaea gradually broke apart, and evolution followed different paths on different continents. The large Argentinian quadrupeds exhibit a very unusual development. *Amargasaurus cazaui*, with spines on its back that were many metres in length, was more dragon-like than any other animal that ever roamed the earth. Yet, even this large quadruped was a peaceful herbivore. Its harmless, pencil-shaped teeth were suitable for raking the needles off of the branches of conifers.

GIANTS

The large quadrupeds took advantage of an environmental niche that boasted extremely lush vegetation. Gymnosperms and Cryptogams grew in assorted habitats ranging from warm to cold and from humid to dry, thus offering plenty of opportunities. Co-evolution may have resulted in huge forms such as Argentinosaurus, which was a total of of 36 metres long and stood more than 6 metres high at the shoulder. The neck and front legs of this dinosaur barely fit in the exhibition hall in Naturalis. Argentinosaurus is the largest dinosaur ever found, and the animal survived on a diet of plants. This giant must have eaten as much as 2000 kilograms of plants each day with its pencil-shaped teeth. Imagine a kind of race between plants and such gigantic animals. As the trees grew ever taller, the creatures that depended on these trees for food had to follow suit. This might explain why the animals grew so tall.

MIGRANTS

The Ornithischians (bird-hipped dinosaurs) also show a remarkable evolution. According to the famous Argentinian palaeontologist Bonaparte, the main difference between the North American and South American dinosaurs is the relative dominance of the Saurischians in South America. Consequently, the Dino Argentino exhibition has only a few Ornithischians on display. Of the few Ornithischians remains encountered in South America, one species tells a spectacular story: it migrated from North America! Remains of a close relative have been found in the state of New Mexico, in the southwestern part of the United States. The Argentinian specimen was found as far south as Patagonia, and may be considered a second-generation migrant. It has been called *Kritosaurus australis* (i.e., the noble reptile from the south). No matter how noble, Kritosaurs were herd animals that were well adapted to migration and had small hooves. The front legs were slightly shorter than the hind legs, enabling the creatures to lean on their front legs while they were grazing. In the face of danger, however, they could rapidly flee on their hind legs; basically, this group could not really make up its mind whether to become bipedal or quadrupedal.

SEXY ACCESSORIES

In one group, the Hadrosaurs, sexual selection is believed to have played a major role in evolution. Hadrosaurs exhibit a very large variety of body ornamentation: females may have preferred males with unusual spines or with collars that bore many protrusions, or the males may have battled for the right of first choice of female. Thus, sexual preferences gave rise to new lineages in different environments.

THE UNFORESEEN

The dinosaurs are generally considered to exemplify a group that enjoyed many advantages. These advantages enabled them to make better use of the available opportunities than any other animals. It must have taken an exceptional and unusual disadvantage to turn such a gradually built-up success formula into a recipe for failure and disaster. This unusual disadvantage measured 10 kilometres in diameter and hit the Earth 65 million years ago in Yucatan. Its impact caused a major change in climate and the rise of flowering plants. Thus, the niche that favoured the dinosaurs was destroyed. Suddenly, mammals and birds were better adapted than reptiles to populate the now barren niche. For them, Cruijff's law also applied: 'Every disadvantage has its advantage'!

Can Dinosaurs Survive?

The Future of the Pharmaceutical Industry

How does the future of the pharmaceutical industry look? A selective group of experts with experience in drug research and development gave their views from between the fossilised remains of the giant lizzards of the past – in a symposium held in the Dutch National Museum of Natural History in Leiden. They discussed opportunities, chances and threats, both for the industry and for drug development. The CHDR-organised meeting was chaired by Professor of Pharmacology Douwe Breimer, Rector Magnificus of Leiden University.

The typical multinational pharmaceutical corporation is often compared with a dinosaur: large, threatening, immensely powerful, and frightening to many people. Yet, we all know what happened to the dinosaurs. Although the reason behind their extinction is unknown, theories range from climate change resulting from a meteor collision with Earth to their bodies outgrowing their tiny brains. Worries about the survival of the pharmaceutical industry are widespread and fed by a diminishing number of innovative compounds appearing on the market at an ever-increasing cost of development.

The current situation is in part the logical result of a number of developments that might be considered inevitable. Many diseases are now cured or well controlled by medicines that have few side effects. Most infections and many cardiovascular and gastrointestinal diseases have been effectively harnessed. With these low-hanging fruits picked, we are now left with chronic diseases with the most complicated pathophysiology (e.g., cancer, diabetes, arteriosclerosis, dementia, and neuropsychiatric diseases). It is difficult to find new therapeutic interventions, and difficult to develop them.

Although the spectacular developments in genetics and in the general understanding of biological complexity should eventually make it easier to find new treatments, initially, they simply provide potential targets for intervention. Contrary to earlier, well-established, physiological target mechanisms, these potential targets are largely unvalidated. In other words, we have no idea what they mean in relation to the diseases under study. To determine whether an intervention affecting one of these targets has clinical value, the target must be developed right to Phase IV. This huge risk must be taken because the current predictive models in animals and humans are particularly poor for these difficult disease targets.

There are also additional factors. Society has become much more safety-conscious, and the environment of drug development has become highly regulated as people in general have become more assertive and litigious. In addition, the quality standards for the development process have evolved to almost zero fault tolerance, in line with similar developments in other industries (e.g., the engineering industry).

This series of challenges is complemented by global downward pressure on drug pricing. As this pressure increases, incremental innovation regarding existing products to stop the erosion of turnover by generic drugs will be difficult, as decision-makers (which, incidentally, are increasingly insurance companies or governmental bodies rather than physicians) will simply not tolerate any price premium. Real innovation, defined as satisfying a big medical need, is by far the best assurance of large profit margins. However, this route closes the loop, since the other factors that I have discussed have so strongly increased the risk of real innovation that this option is increasingly unattractive.

The global pharmaceutical industry has only managed to shepherd 10 innovative products to market, despite aggregate spending on R&D of a staggering $30 billion US. This result is not surprising in view of the factors already mentioned.

Is this the end of the pharmaceutical industry? Probably not, but it is a clear signal that larger changes are necessary, beyond the odd merger to increase market share. Many other branches of industry have faced situations like this and emerged stronger and more profitable. Currently, real revolutionary and innovative solutions are still rare.

To discuss the issues mentioned above, the Centre for Human Drug Research organised a symposium that was attended by a selective group of experts with experience in drug

research and development. This symposium was held in Leiden, and chaired by Professor of Pharmacology Douwe Breimer, Rector Magnificus of Leiden University. The group also contained a number of young researchers in the industry. To inspire (and perhaps frighten) the group, the meeting took place not the familiar environment of a conference hall, but in the Dutch National Museum of Natural History, and coincided with a major exhibition about dinosaurs.

FACTS AND FIGURES

Steve Arlington, Global Head of Pharma from IBM Business Consulting Services, provided some facts and figures about the current state of the pharmaceutical industry. His company's new report, Pharma 2010: The Threshold of Innovation, showed that between 1990 and 1997 the value of the pharmaceutical industry as measured by its capitalisation rose by 350%; in the 2 years between the end of 1997 and 2000, that value dropped by almost one-half. When discussing the then-future of the industry, he asserted: 'Analysts believe that the industry will grow at 9% per year for the next 8 years. But this number is being based on wishful thinking. The pipeline with new drugs is pretty bare. There's only fourteen blockbusters in it between now and 2007, drugs that will make $1 billion or more, assuming that those compounds actually get through. You and I know what the attrition rate looks like. So there's no way that 9% can be reached. My organization believes that growth in today's model of the pharmaceutical industry will not beat 5.3%.'

Arlington also drew attention to some disturbing numbers about the patent expiry position of the industry: 'Between now and 2007, 35 drugs with a global sales value of $73 billion will come off of patent. To stand still, the industry will have to fill this hole. And $73 billion is a very big number and the industry doesn't have much hope given the pipeline.'

He added another $11 billion for the Phase II and Phase III failures of the last 3 years that never reached the market: 'Frankly, the analysts had already put it in the share price that they would be going to make it to the marketplace.' And the story about the $84 billion gap was not the only worrisome news Arlington had to share: 'The drug industry makes most of its money in the North American shores; 67% of blockbusters in the world are sold in the US. It is an ever-decreasing number of drugs with an ever-increasing concentration in the geography.' More importantly, he warned that the impetus of innovation is no longer with the drug industry: 'When the pharma industry brings a new drug to the marketplace, it proves it's efficacious and it proves it works on patients. But the rise of power of the managed care organizations in the US market has switched the power base to who defines who and what will be paid for a drug. Today the insurance business or the managed care organizations and health care providers define what is efficacious, what should be developed and what should be paid for. Therefore the profit that a company can make in the world's largest drug market and the level of freedom they've got is altered. Hence a prediction of the annual growth rate of 5.3% and not 9% is realistic.'

English pharmaceutical consultant Dr. John Posner thought it was too early to conclude that the age of blockbusters is over: 'There are plenty of opportunities for blockbusters in the future whether it is for cancer, rheumatoid arthritis or the diseases of old age because we are on average living longer, whether it is for Alzheimer's, whether it is because we overeat and develop diabetes. Saying the fruits before were lower hanging and now they are higher up in the tree, doesn't mean that anything that was done 20 to 30 years ago by people like Paul Janssen and James Black was easy by any means. Those discoveries have been tough.'

However, the discussants agreed there would not be enough blockbusters to provide big companies with a respectable growth rate. '[The] pharmaceutical industry has realised it can't grow through drug development, it has got to grow through acquisition', said Dr. Philip Brown, publisher of Scrip Magazine. 'I asked an analyst why Pfizer acquired Pharmacia. He said it was cash. The addition of Pfizer to Pharmacea would improve Pfizer's cash flow by approximately $10 billion a year. If you add Warner Lambert into that as well, they had an additional cash flow prior to those two mergers of $30 billion. This would give them 11% share of market.'

Brown expects that within 10 years, there will only be five big pharmaceutical companies left, each with approximately a 10% to 12% share of market: 'Where they go beyond that is another question. Maybe [the] pharma industry will go the same way as the motor car industry. It will in fact be dominated by huge companies and whether they grow by research and development or by other matters becomes irrelevant, because there are so few of them. The competition element will disappear. So I think that we are looking at R&D in a different environment than we looked at it before.'

Professor Dr. Adam Cohen, Director of the Centre for Human Drug Research in Leiden, criticised the comparison with the automotive industry: 'In a motor car company, you can innovate by incremental innovation, you put a new air conditioner in an old model. But you can't do that with a drug. You have to redesign the whole car as you develop a new drug.'

R&D CLIMATE

Philip Brown has discussed how mergers and acquisitions have had a devastating effect on Research and Development: 'When Glaxo and Wellcome merged, there was a hiatus of 6 to 9 months while they tried to sort out what were the right products for doing their R&D on. This led to prioritisations of the R&D projects, but then of course all the scientists who were doing that had left, so they had a small problem. That happened again with the merging with SmithKline Beecham. I am not surprised that the pipeline with new drugs is bare because they haven't been doing any research and development for any length of time since these mergers happened.'

Mergers are not the only reason that scientists turn their backs on careers in the pharmaceutical industry. John Posner believes that the whole atmosphere is wrong: 'Within the R&D organizations, a non-scientific, even anti-scientific attitude has developed. The people who really go out and discover new molecules are lost, they are not valued and there is not even an attempt to hold on to them. This seems extraordinary, this is the most important asset you have. Companies are risk-averse, they don't want awkward buggers, the people who can call all good questions. They don't want people who are gonna rock the boat, and yet, if you are in an environment in which R&D is to flourish, these are the sort of people you need.'

Small companies and some biotechnology firms have a different attitude toward scientists, Posner said: 'You can go in there and within 10 minutes you are sitting at a table with all the key players and you are having a serious scientific debate. Try and do that in a big company. A very small fraction of the time within the companies is spent actually talking about serious science. Companies are process-driven, they are not data- or hypothesis-driven; process is bureaucracy and all that goes with that.'

Dr. Andreas Wallnöfer of Hoffman-La Roche admitted that there is a lot of focus on process inside his company: 'It's a focus on management solutions. Almost every semester a consultancy group shows up in our offices to advise us how we could be more efficient in our processes. Maybe we also need new business models to allow better creativity in smaller units.'

At present, Philip Brown has only seen attempts to take the creativity out of R&D: '[The] pharmaceutical industry tries to transfer it into some kind of supertechnology. But is not. You can do combinatorial chemistry – [it] doesn't matter how many powers of ten you want, there is a machine that will do it – but that is not the way to find the world's leading drugs. It is the antithesis of research. The quality of the research staff is extremely important, these are people that need to have an environment |in which they can do research and maintain the tenacity.'

Sir James Black, a Nobel Prize winner for Physiology or Medicine in 1988, described the scientific attitude of drug inventors in the good old days: 'What is it what people like Paul Ehrlich and Paul Janssen did? They started with a conception, which was unique to a person, there wasn't a committee decision, it didn't come corporately, it was one man, with an idea and a passion. Both of them concentrated, they didn't allow their attention to be distracted; there was total commitment. They kept going as long as was necessary to achieve that purpose. And finally of course both of them had this act of creation. The first act in this business is a chemical, which you can patent, but the second creative act is that judgemental choice of a molecule that looks as though it might make the grade. One thing we don't know is how long it's going to take. And that has been the problem with the industry: it has become impatient, it couldn't stand the long lines of this steady, iterative, evolutionary selectionist type of activity, so they went for numbers, and in that business there has been something of the wrongdoing.'

John Posner noticed that companies have become very risk-averse: 'They are prepared to kill drugs before they have even been adequately tested, before they have even learned something from them. But if it was considered good enough in the first place to invent a molecule, protein or whatever it is, surely it is good enough to learn something from it and to pursue it until it is quite clear that it needs to stop. So my plea to the industry is about creating the right environment to allow scientists to flourish both at the discovery end and in the development.'

Dr. Piet Hein van der Graaf, Director of Discovery Biology at Pfizer Global Research & Development in the United Kingdom, admitted there is very serious attrition: 'My main concern is how to increase the success rate from idea to proof of concept. A lot of organizations have lost the plot and have thrown overboard skills, expertise, and people that were actually bringing the successes before that. So hence, there has been an extreme focus on components and not on systems. But in my environment, I certainly see a huge shift. If you look at the human genome in terms of druggable GPCRs and enzymes, there is a large number which we don't know the function of, but that look inherently druggable. The number of unexploited targets greatly exceeds the number of targets we have currently exploited. So I am optimistic, there is hope.'

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Arlington was skeptical: 'If we continue to screen molecules using the fastest ultra-high-throughput screening technologies we have got, it would take 10,000 years if we have 500,000 targets, roughly. The bottom line is you can't use chemical screening technologies to go forward, you have to get into what Ehrlich did.' Van der Graaf thought the figure of 500,000 druggable targets was an exaggerated one: 'It's a lot less. I don't see high-throughput screening as the bad guy you shouldn't come near. It's a complementary methodology, which sometimes is a useful first filter. A drug won't be launched just on the basis of a high-throughput screening result.'

REGULATORY HURDLES

Dr. Paul Janssen, the drug inventor that founded Janssen Pharmaceutica in 1953, opined that bureaucracy was the outcome of the thalidomide case at the beginning of the 1960s: 'When I was young, to discover and develop a new drug took 2 years. And I thought that 2 years was already very long, but of course the number of bureaucrats who had to make up their minds on whether this new drug was worth something or nothing, was limited. But then came the prohibition on thalidomide, and the FDA was set up to protect America against the evils of drugs. And the American people believed this was possible. All the problems I'm seeing now are almost the direct consequence of what happened then. The average cost of development of one new drug has reached the figure of $1 billion. That's the same as committing suicide. Why do we allow this to happen? It's obviously against the interest of everybody, except maybe some bureaucrats.'

Janssen said the meaning of the word 'obviousness' has been lost: 'If the effect of a new drug is not obvious, which is the case with many drugs, then I am simply not interested, and neither is the patient, and we simply shouldn't pursue it. Why do we need these very expensive trials of 15,000 patients? Simply because the effects we are talking about are so small, that in order to get a p-value lower than 5% you need thousands and thousands of patients. This is an organized lie in my view.'

Cohen agreed that a lot of money is wasted in drug development, and echoed Janssen's discussion of the value of 'obvious' treatments: 'Look at a recent paper in The Lancet that compares the receptor antagonist losartan to ACE inhibitor captopril in 5,000 patients, costing about $17 million. If someone would have asked us to guess if losartan was superior the answer would have been no, because we understand that bit of physiology reasonably well. It isn't superior and I would think that is a $17 million waste. A shift towards using that money for much more relevant research on drugs that work obviously, is one of the most important shifts we need.'

Wallnöfer complained about the cooperation between regulatory authorities and industry: 'We experience increased regulatory hurdles daily. Of course it's in the interest of the consumer to be sure new products are really safe. But there's also a tendency of bureaucracy that makes it very hard to interact with these authorities.'

Dr. Dana Hilt, Vice President of Clinical Development and Drug Metabolism at Guilford Pharmaceuticals in Baltimore, noted that the regulatory environment is highly risk-averse, particularly in the United States: 'There is increasing emphasis on larger numbers of patients, more extensive trials, more extensive examinations of subpopulations of patients, drug interactions, in all possible situations, to allow the marketing of a drug. Companies have to raise the hurdle in the regulatory environment to please the regulators. It would be helpful if we could put the regulatory authorities in a position of working with us instead of at odds with one another more. Yet, if something goes wrong after the drug was marketed, they are brought in front of our US Congress and they are asked the question of why they allowed this drug on the American market.'

DISEASES, NOT COMPOUNDS

The industry is also wrestling with its own negative image. According to Arlington: 'If you ask your children which industry they would like to go in, they don't say, 'I want to go and discover brilliant new drugs to save the human race', because that's not the way the pharmaceutical industry has been painted in the press. Just look at the news last year about

A Dana Hilt muses on the words of Paul jansen. John Posner attentive.
B Consultant and CHDR PhD Bert Tuk to be eaten by a dinosaur
C Skeletons to inspire the meeting ttendants
D Douwe Breimer and Adam Cohen
E Piet Hein van der Graaf listening to Don Stanski
F John Posner, Steve Arlington
G The full meeting and the ever watchful dino's
H Jim Black, Douwe Breimer Adam Cohen and Philip Brown

the industry and AIDS drugs in South Africa. The industry today is a pariah, it has been starved of the brightest brains and the best talents of our medical schools. I don't believe the industry deserves that, it's one of the best industries in the world to go and learn in. So that balance must be redressed to get the very best talents back in the industry.'

Cohen confirmed Arlington's analysis: 'None of our research fellows end up in [the] pharmaceutical industry. Unfortunately, because there is a lot for them to do. The inspiration which one needs to attract people is to treat diseases rather than to make compounds. At the moment, we are only evaluating drugs that have something to do with a target. But we know very little about this target and what it has to do with the disease itself. The sort of discussions we have with companies are mainly about how fast we can do our experiments for them: it has to start in week 46 and not in week 47; we have discussions about if all the sodium we measure in these subjects will be in the computer on the right day; and we can have discussions about what sort of meal they take. And the discussion we don't have, and this has started to disturb us increasingly over the last couple of years: what is it really that this drug has to do with the disease? We had a huge discussion in The Netherlands about thrombosis and third-generation pills. We talked a lot about the risks, but why didn't we concentrate on the molecular mechanism of how you actually get thrombosis from oestrogens, which begs to be discovered?'

Dr. Fred Falkenburg, Professor of Hematology at the Leiden University Medical Center, has experienced how difficult it is to interest large pharmaceutical companies in curing a disease. He treats cancer patients with allogenic stem cell transplantation, a method that can cure about 30% of individuals under 16 years of age who fail to respond to chemotherapy. He notes: 'We are not talking about a simple compound, but about a procedure that exploits the use of cells from a donor to treat the malignancy. The main advantage of this procedure is that you introduce a living cell into an individual that will live there for quite some time and do its work. From a conceptual point of view, [this is] very interesting and completely new to pharmaceutical industries. They don't work with living things, but with molecules.'

Although people at the top of the pharmaceutical giants were interested, at the initial meetings they immediately started to talk about commercial exploration. At first, Falkenburg made the mistake of saying he was not really interested in the commercial part of the endeavour. 'A severe sin if you talk with pharmaceutical companies, but also if you talk with people from the government and regulatory people. They think that if it is not directly commercially interesting it is probably stupid and will not work. So we picked out a few things in this whole procedure that might be patentable, and asked pharmaceutical companies if they would like to develop this with us, to make this treatment more rapidly available for a larger number of people. But middle management in the companies didn't want to cooperate, because it is too complex in their minds that you develop something that may not directly pay off. If you come up with science, industry is not really interested, so I stopped these visits. I have to find other ways, maybe private individuals will give us money.'

Dr. Donald Stanski, Professor of Anesthesia at Stanford University, understood the companies' dilemma: 'Studying diseases may not make money, and if companies don't add value, they don't survive. The marketplace dictates that. The cost of understanding Alzheimer's disease is so high and so long that the likelihood of any one pharmaceutical company to do that is extremely low.'

Falkenburg agreed that it is unrealistic to ask pharmaceutical companies to help solve the problem of Alzheimer's as long as that disease is not understood. Such an undertaking 'may take 25 years, and people don't want to wait that long for a return in investment. But there are several diseases where we can come close to a solution in about 5 to 7 years. And it's even impossible to find investors for that middle-long approach. Not only in industry, but also in academia. We can only improve the whole system if we can take more time to solve bigger issues, and that has to be done both in academia and in pharmaceutical companies'.

THE FUTURE

Cohen agreed that more cooperation is needed between academia and industry: 'The example of Fred Falkenburg shows the systems are currently so disjointed that it is impossible to come through in organizations. The amount of knowledge we have spread out through universities and drug companies is huge, but we don't do anything with it. Knowledge within the companies is disintegrated and it can never be used in a proper way. Within universities we have the same problem. The demand for integration is where the barrier lies. And that's also where the possible means of survival lies. We still need the drive of the individuals, as James Black said, but they need to work together even more than they used to. We have to find models that are beyond the traditional ones, which are funded by people from the stock market, or we need to find new ways of funding [research]'.

Chairman Douwe Breimer said that academia needs a bridging of ideas towards the marketplace: 'A scientist has to remain a good scientist, but has to be assisted by people with other skills to actually make it happen. Academia is still not sufficiently aware of the value of intellectual property, for instance. That is where it starts, and where a different kind of mindset has to be developed. It has to start in the education, where we must teach what it is to be a scientist and what he can mean in terms of benefit for mankind. The message should be that the most inspiring thing for a young scientist is that his invention is ultimately going to the marketplace.'

Stanski thinks industry will have to work with new types of project teams: 'The next generation of people in the industry may in fact be teams of people with different skills and basis, brought together such that the sum of what they do is more rewarding. For example, you have a biologist linked with an engineer and a statistician, and together the three of them can handle information, can handle biology, and can create process in a way that neither one of them has been trained to do[...] Universities are not training [students to master] these tripartite type of skills. In fact, the industry [...] is in a fractured way creating the educational talent and providing the next generation of post-doctoral training. In the end, we will be amalgamating the talent and other specialties to create the kind of innovation that we need, to create innovative working environments that are satisfying for people.'

Stanski sees the industry disaggregating into three parts that separately handle drug discovery, development, and commercialisation. 'At discovery, we have the biotech firms as the prototype of innovation. And the commercialisation will be done by the remnants of the current pharma industry, the few that manage to survive in terms of large sales forces, basically selling and distributing the information of approved drugs.' But Stanski believes that the sweet spot of change will be in clinical development: 'To change that, we need completely new organizations. The difference is going to be basically in the dealing [with] and handling of clinical information, and in making better decisions, ultimately. Step back and look [at] what was successful about what Dr. Paul Janssen did: as CEO, he knew and understood the information available in his company and could base decisions on that. In that way, he was able to develop 70 drugs in 30 years'.

Stanski also pointed out that the ability to fully understand the available information has been lost: 'As information is handed off, half of it gets lost. And as it's lost, then it has to be rediscovered, and in this process bad decisions are made. We need new ways of handling information – using quantitative techniques, using models, using informatics – to basically distill and summarise the clinical information to prevent the silo effect which we see.' James Black said that industry has to switch to system analysis and biomathematics: 'If the industry keeps looking for components, they are not going to win. The diseases we now try to understand are system failures, not component failures. High blood pressure is a system failure, septic shock is a system failure. The way that you control these kinds of failures is by combination of drugs.'

In the future, Stanski expects that companies will scale down. 'You will get distributed organisations, in which you keep the critical thinking internally. All of the external execution becomes purchased as needed in a competitive manner.' He recognises that the most difficult part is how to fund this new drug development structure. 'The current capital markets aren't set up to do that very well. We don't yet have next-generation funding mechanisms for clinical development that would allow the concept that I have to be played out.'

Arlington wondered exactly what event might catalyse the transformation of the pharmaceutical industry: 'I have made my life's work of trying to let people look in the mirror in the pharmaceutical industry, but I'm not sure I'm going to succeed. I have never met more conservative individuals in my life than in those companies. And we are asking them to transform and change their business. Not in my lifetime, would be my comment. I don't know what we will have to do to get the message through, but it's a very important message to mankind.'

Stanski knew the eventual solution: an equivalent of the asteroid that killed the dinosaurs: 'This will be found in the introduction of price controls in the United States. That probably won't happen in the Bush administration, but in another 3 years and after some wars, the American people will probably be so fed up with the increasing costs and decreasing quality of health care that the asteroid of price controls will hit the earth, causing a massive death and shakeout of this industry.'

John Posner put an end to all speculation about the future: 'Prophesying is a dangerous business. If we would have been sitting around this table 65 million years ago, I would suggest the one thing we would not have predicted would be the death of the dinosaurs due to an asteroid. And even if we had managed to do that, we certainly wouldn't have predicted that turtles and birds would survive.'

PART TWO

Long storylines

The 25-year history of CHDR of course rests on the shoulders of giants, whom you will find in this partly photographic history of the Foundation. The history is also characterised by developments of a much longer duration than originally intended, which sometimes led to unexpected results.

The (pre)history of clinical pharmacology in Leiden

TAKING A LARGE JUMP IN TIME, WE GO FROM THE ERA OF THE DINOSAURS TO (ALMOST) HISTORICAL TIMES: THE EARLY 1970S. THAT'S WHERE THE STORY OF CLINICAL PHARMACOLOGY AT LEIDEN UNIVERSITY (ALMOST) BEGINS. BUT PLEASE PAY ATTENTION, BECAUSE FROM THAT MOMENT ON, THINGS WENT VERY RAPIDLY.

A review of the records of the budding department of clinical pharmacology in Leiden between 1970 and 1984 is in many ways amusing, but also slightly disconcerting. They reflect the predominant behaviour of academic medical institutions at the time. A multitude of reports, memos, and commentaries try to define the specialty, the specialists, and the space in which work was conducted (an estimated surface area of 75 m2 in 1970). Although the need for multidisciplinarity occasionally emerges, the different departments largely talk about their own turf. The patient rarely appears; students, training, and education are mentioned only in passing. Many of the discussions were more about who should be the clinical pharmacologist (a vociferous school stated that these should only be internists) than what clinical pharmacology would be required to gain knowledge about the epidemic of new medicines that was hitting the field in the 1970s.

Herman Mattie, who trained with Desmond Laurence in London, ran the small department. Although his research was originally general clinical (human) pharmacology, it had evolved into the clinical pharmacokinetics and dynamics of antibiotics. This was not really because Herman wanted that evolution, but rather because the pressure of continuous disputes between different factions made a more general approach impossible. By 1984, clinical pharmacology was abolished in Leiden, and Herman Mattie ended the meetings of the working group for this specialty.

At the time, there was a traditional department of pharmacology in the medical faculty that organised a second year pharmacology course for the medical students. The department's research was largely in animal pharmacology; although of course there were some links with the hospital, these were fairly limited, in line with the situation in most of the world. This would soon change.

PHARMACY BECOMES BIO-PHARMACEUTICAL SCIENCES

Leiden also had a faculty of pharmacy that trained pharmacists and had a research interest in medicines before they were administered. Analysis of drug concentrations and dosage forms, pharmaceutical technology, and medicinal chemistry

Hidden behind shrubbery with unknown pharmacological potential, this was CHDR headquarters in the early days. Few people would dream of the enormous developments and the futuristic buildings that lay.

Inside building 50a. PhD student Jean Griensven takes a phone call. José Witteman, one of the first nurses employed by CHDR, is busy at her desk. Everything is in perfect order, state-of-the-art early 1990s but obviously not GCP 2013.

A forearm blood flow experiment to study the effects of drugs on vascular function. The setup is still used today, albeit with equipment that looks fancier – and thank heavens we have got rid of all those power cords.

Eiji Uchida, Professor of Clinical Pharmacology at Showa University Medical School was actually an immortal Dutch saint in his younger years when a research fellow at CHDR. Top secret!

Professor Uchida still is quite a fan of the Netherlands, as shown here by his orange tie. To his left side professor Balkenende, who was prime minister during most of this millennium.

Life in the Netherlands can be challenging and even dangerous to citizens from more organised countries like Switzerland. Here Roche visiting scientist Andreas Wallnöfer seems to be in need of resuscitation. Thanks to the efforts of (from left to right) Jean van Griensven, Jeroen van Rooy and Adam Cohen, he managed to survive.

were the main areas of research. The focus changed around the 1970s, when the application of gas chromatography, liquid chromatography, and immunoassays made it possible to measure the drug concentrations in biological fluids. The findings were spectacular. Drugs that were supposed to be rapidly acting circulated in the body for much longer than expected, and for some the variability with which they appeared in the bloodstream was shocking. This variation was sometimes due to badly made tablets - a brand-new discovery at the time.

Douwe Breimer (who will appear again in this story) was a PhD fellow in Nijmegen, and was studying the pharmacokinetics of hypnotic drugs, such as barbiturates and benzodiazepines. This research required studies in humans, both healthy volunteers and patients, and Douwe was performing this research as a pharmacist. He became professor of Pharmacology in the faculty of Pharmacy in Leiden in 1976; Adam Cohen recalls that their first meeting took place shortly after his inaugural lecture in October of that year.

In the following years, Breimer built a line of research regarding the variability of drug concentrations and drug responses. In 1984, it was decided that too many pharmacists had been trained in the Netherlands and the faculty in Leiden had to change. Douwe turned this threat into an opportunity by founding the Centre for Bio-Pharmaceutical Sciences, thereby definitely changing focus from the drug before it was administered to the fate and actions of the drug after it entered a biological species, including humans. Douwe managed this research through associations with individual physicians in the University Hospital and produced a series of very good scientific studies. Such collaborations had previously been considered impossible, and constituted the first demonstration of the synergy that could be achieved.

CONTRACTION LEADS TO GROWTH: THE EMERGENCE OF CHDR

The closure of the faculty of Pharmacy in Leiden was the result of a momentous level of cutbacks, which occasionally occur in governmental finance and may be familiar to the reader in 2013. It was (perhaps a little cryptically) called Task Division and Concentration (TVC in Dutch, for Taakverdeling en Concentratie). Wim Deetman, then minister of Education, wanted to reduce university budgets by 300 million guilders. But he wanted more than just a budget cut: the reduction had to be associated alongside an increase in quality. Of course, the details of how this grand ambition was to be accomplished were left to the victims of the operation. The clamour throughout the country – the operation led to 4000-5000 job cuts – was considerable.

However, there was also some light in this darkness. As a result of the cuts, there was some money available for new initiatives. Ed Broekhuizen (who, as a financial manager at Leiden University, had been involved in the creation of the Centre for Bio-Pharmaceutical Sciences) had moved to a high-ranking position at the Ministry of Science and Education, and warned Douwe Breimer about the possibility of developing something new.

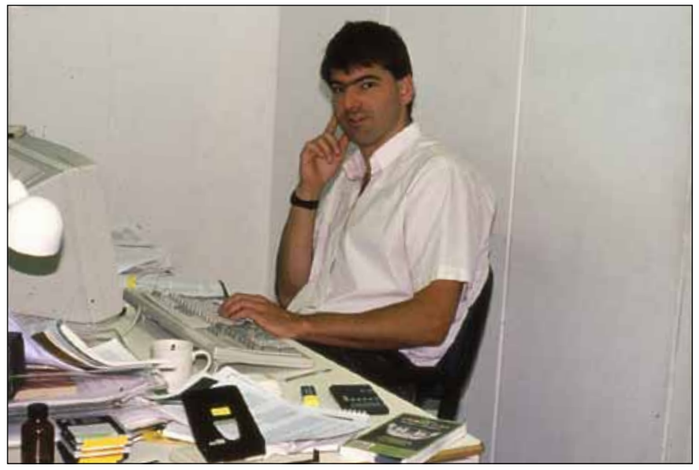
A proposal for a human research unit, to be developed at Leiden University Hospital, was rapidly put together and sent in on 11 April 1986; the positive response of the Ministry came on 8 July 1986. Leiden was to receive 1.3 million guilders to set up a Centre for Human Drug Research, and a yearly subsidy of 900,000 guilders to be continued for at least 6 years on condition of evaluations in 1987 and 1990. Although the Centre was initially intended to be a department in the hospital, this set-up was considered too risky because the hospital's Supervisory Board was concerned that testing medicines might easily lead to damage to their reputation. Therefore, it was decided that CHDR would become a research foundation.

SPACE FOR CLINICAL PHARMACOLOGICAL RESEARCH

When one reviews the proposal that was made to the Ministry for CHDR today, it is attractively and surprisingly short: no business plans, no SWAT analysis, and the whole thing was no more than four A4 pages. The Ministry's answer was even shorter. Such an informal approach is refreshing in retrospect, as it signals unprecedented freedom and creative space that we never encounter now. Today, such an initiative would require extensive plans containing precise descriptions of how the money was going to be spent, with detailed divisions between personnel and material expenses.

The subsidy was announced in Cicero, the magazine of Leiden University Hospital in 1986. 'You want to know how fast a drug is absorbed in the body and how fast it is excreted,' explained Douwe Breimer. 'Only then can you know when to give the next dose of a drug. We are also studying what the relation is between the concentration of the drug in the blood and its actions and side effects.' There was also interest from the pharmaceutical industry, and Dolf Schweitzer, the medical director of the hospital did not immediately reject this, 'but the share of this research must be only a small fraction of the total.' 'We want to do research to develop new drugs. Not contract research,' added Douwe Breimer. Breimer and Schweitzer then went on to say that they hoped to appoint a physician with a PhD in pharmacology to assume the daily management of the project as soon as possible.

Exploration knows no boundaries. Here, PhD student Fred van Steveninck and industry scientist Andreas Wallnöfer are ready to explore the Californian highways in a red convertible, while also studying the effects of hair colour and gender on the intelligence of Swiss citizens.



The scientist in his natural biotope: Fred van Steveninck, the first research fellow of CHDR. Please notice the essential paraphernalia: coffee, a stimulating array of papers, mineral water, books and unknown sources of data. We can only speculate about the contents of the brown medicine bottle.

CHDR has always been known for a hands-on approach. In the first building, staff scientists even contributed to renovation activities. Joop van Gerven in full DIY mode. Rumours that he was experimenting with skull trepanation could not be corroborated by reliable witnesses.

The kitchen was the very heart of building 50 A. This is where plans were made, meals were eaten, meals were prepared for volunteers, jokes were shared. The spirit of this kitchen is still alive, even if its location has long been reduced to rubble. From left to right: Nidhi Srivastava, Joop van Gerven, Jean van Griensven, Anja van Vliet, Koos Burggraaf, Fred van Steveninck, Annet van der Jagt.

There were signs that a new building was badly needed. Here, mrs Marijke van der Mey has found a creative solution to expand her desk space. The carpet with its highly expressive patterns of cafeinated pigment has later been sold to a Jackson Pollock fan.

An expedition in Leiden's venomous swamps and uncharted regions led to the discovery of the perfect location for CHDR's next building.

As soon as the subsidy was announced, a number of staff were transferred to CHDR. Ton de Boer (now Professor of Pharmacotherapy at the Utrecht School of Pharmacy) was working with Meindert Danhof on drug interactions of anticoagulants. This work, performed under the supervision of internist Johan Boeijenga, was transferred to CHDR. Lab technician Ria Kroon (now Operational Director at CHDR) also joined the team and was conducting HPLC drug measurements for Ton's project.

SEARCH FOR A DIRECTOR OF THE FOUNDATION

In 1986, Adam Cohen worked for the Wellcome Research Laboratories in Beckenham, Kent, where he was employed by Wellcome Biotech (one of the first biotechnology companies in the world) to develop a fibrinolytic protein. In Leiden, he had studied pharmacy and medicine, and had been a student assistant in the small department of Herman Mattie. Starting in 1981, he was in England, at Wellcome and in internal medicine training at King's College Hospital and Dulwich Hospital. He had written his PhD thesis with Douwe Breimer and Erik Noach in Leiden about work he did in Wellcome with Tony Peck and Arthur Fowle.

Adam recalls: 'I had tried to get Douwe to come to Wellcome to lecture, but he never found the time, so when he suddenly called me to say he wanted to come over I was quite surprised. Anyway, he arrived, was given lunch, gave his lecture and I showed him around the labs, when he asked me if I would be interested in a job in Leiden. As a matter of fact I was. Wellcome had just made the transition from a Foundation to a quoted company and was going through a number of reorganisations. I had decided that I did not want to go to the US company, and the fibrinolytic project was coming to an end because of a patent problem. Additionally, we wanted Danielle and Sophie (then 4 and 2) to grow up in the Netherlands. So I went for a series of interviews. Around Christmas 1986, I heard I had the job at around 50% of my salary at Wellcome, but we were very happy anyway! We moved back around May 1987.'

THE EARLY DAYS: BUILDING 50A

The building intended for CHDR was a temporary extension to what is now known as the 'Poortgebouw' (the former administration building of the Academic Hopital. CHDR was to occupy this extension, the previous location of the hospital pharmacy, which had just moved to the new hospital building. During January 1987, this wooden temporary building was changed into a small clinical research unit, very much based upon the Wellcome unit in Beckenham. There were four beds, a sitting area for the subjects, and the old cold room of the pharmacy was changed into a CNS measurement room. There also was a laboratory (where Ria Kroon operated the HPLC machine), as well as some offices.

When you entered the building you could not miss the kitchen – and there was always someone sitting at the kitchen table drinking coffee. This was also the general meeting place, although the meetings were still infrequent, agenda-free, and short. The initial team consisted of Ton de Boer, Ria Kroon, and Adam Cohen, who were soon joined by two research nurses, Anja van Vliet and Annet van der Jagt. Anja and Annet were intensive care nurses from LUMC. Margreet ten Kate (now HR manager at CHDR) joined soon after to take over the secretarial work.

The early days also established the culture of CHDR: open, informal, highly professional, without much respect for age-determined hierarchy, but highly deferential to scientific or operational expertise. Clinical scientists from many disciplines visited the building, and it rapidly became an informal meeting place. Interestingly, this culture has been maintained throughout the years to the present day.

The subsidy was used to equip the unit properly, and Ton de Boer often recalls an amusing meeting with a vendor of cardiac monitoring equipment: 'Adam and I were still quite young and equipment salesmen did not know that we were quite able to buy and to decide without the usual long procedures in hospitals. A salesman was demonstrating ECG equipment and was attached to a monitor when we started to name our shopping list... we want 4 of these, 2 of those, etc... As Adam did this I watched his heart rate going up quite steeply!'

This team went to work on the first human studies. Initially, these studies were ongoing work for the thesis of Ton de Boer. This was, despite earlier predictions, contract work for Organon; however, it could also be used for Ton's PhD thesis. This 'overlap' between traditional contract work and important science that could also be used to train and educate started to form the strategy of CHDR. At the time, CROs were developing as the operational support for trials, with the science and knowledge residing in companies and universities. To do good clinical science with good operational quality within a single organisation was and is rare. This mode became the CHDR niche: not only good science (as at a university) or good operational quality (as at a traditional CRO), but a unique, dual focus. Ton defended his PhD in 1990, and went on to become a Professor of Pharmacology in the faculty of pharmacy in Utrecht.

VISITORS

In 1988, Eiji Uchida, a young clinical pharmacology researcher, wrote to Douwe Breimer that he wanted to spend some time in the Netherlands and especially at CHDR to learn human phar-

And so it came to pass that a new building was erected for CHDR and the benefit of humankind. It was built in the wastelands of what was to become a blooming Bioscience Park, after we brought civilisation, running water and inspiring new architecture.

In the beginning, as always, there was some degree of chaos. But thanks to the multitasking capabilities of CHDR staff (here Anja van Vliet) this chaos was rapidly channelled and transformed into the level of order and organisation characteristic of CHDR.

In the new building, Marijke van der Meij prefers to use her new desk instead of the surrounding floor.

One of the most popular features of the new building was the terrace. Even if it rained all over Holland, it was sunny and warm.

So many people want to be a test subject at CHDR that sometimes we have to contain them. Here at the square near the Leiden Town Hall, in the introduction week for new students in Leiden.

Quality control also is about finding the right information when needed. One of the first questions you have to answer is of course: what is the standard operating procedure for filing standard operating procedures?

macology. Eiji stayed for 2 years and became a Professor of Clinical Pharmacology at Showa University Medical School after he returned. He has remained a very loyal friend of CHDR and of the Netherlands, which he demonstrates through glowing accounts of expatriate life in Holland during trade missions.

The collaboration with the University Medical Centre in Leiden also started during those first years. There clearly was some hesitation – after all, nobody was used to involving a strange new organisation in 'their' research. The first colleaugue in the hospital to see the value of this collaboration was Edo Meinders, Professor of Internal Medicine. Meinders located a large part of the work of his research fellow, Hanno Pijl, in CHDR. His work on the endocrinology and neural effects of food intake was particularly popular, as the food intake experiments produced a lot of food leftovers that the staff could have for lunch. This collaboration continued with other researchers, and continues today with Hanno as a Professor of Endocrinology.

Collaboration with industry also led to fellowships. Koos Stiekema, an internist working for Organon, wrote his PhD thesis with Douwe Breimer and Adam Cohen. In 1991, Peter van Brummelen (a nephrologist in Leiden) became the head of clinical pharmacology at Roche in Basel. Andreas Wallnöfer was a young electrophysiologist at Roche who wanted to get into the clinical division. Peter felt that Andreas needed practice, and arranged a 1-year research fellowship at CHDR. This training period at least did not stop Andreas becoming global director of early drug development at Roche. He has remained in contact and is a speaker at the 25th anniversary symposium at CHDR.

PEER REVIEW AND CONTINUATION

One condition connected to the CHDR subsidy was that an external evaluation had to take place before the funding from the Ministry of Education became permanent. On 10 June 1991, a peer group of international experts consisting of Professor Charles George (Southampton University), Dr. Nigel Baber (GSK UK), and Professor Frank Gribnau (Nijmegen University) reviewed CHDR in depth. Their positive report led to the decision to continue the funding of CHDR.

At the time the organisation was still quite small, with 15 staff members. There were four research fellows: Fred van Steveninck, MD, for CNS research (now an intensive care specialist in Deventer); Jean van Griensven for the fibrinolytic studies (now a psychiatrist in Utrecht); Koos Burggraaf (now Research Director of CHDR and Professor of Translational Drug Development at Leiden University); and Jeroen van Rooij, who went on to become an ophthalmologist. They all functioned under the supervision of Adam Cohen. In addition there were three nurses.Rik Schoemaker had joined as a statistician/pharmacokineticist, and Jos Hennen ran the computer systems. Such support staff was quite unusual in an academic environment, and when CHDR employed the statistician, Douwe Breimer sighed that it was a sad moment when researchers could not do their own statistics anymore. Rik refused point blank to write a PhD thesis when he joined, but naturally did so anyway in 1999, and is now a PKPD consultant for ExPrimo. Jos stayed the course and has been instrumental in the story of Promasys.

EXPANSION AND BUILDING PLANS

CHDR was there to stay, and ongoing success required adaptations. The temporary building of CHDR was clearly insufficient for modern requirements. Additionally, the Board of CHDR felt that an expansion of the management was required and a new senior staff member should be recruited.

The building plans started with gusto. In a letter from March 1991, CHDR announced to the Board of Leiden University Hospital that new premises would be required by 1992. Initially, plans for a building on the hospital site were developed. As the University Medical Center was moving from many specialty-based buildings to one modern building, there seemed to be enough building space on the hospital site. Discussions and plans expanded. Unfortunately the development company for of the hospital site, Medipark BV, ran into trouble, and by the end of 1993 CHDR had to decide to develop the new building in the Leiden Bio-Science Park and end the relationship with Medipark. The dissolution of this relationship was characterised by considerable turbulence both within the organisation and between CHDR and Medipark BV – but that is a story for another time. The Bio Sciencepark (now the biggest Science Park in the Netherlands) was still a very large green field at that time, and CHDR was to become one of the first tenants.

Building started in June 1994, and the new building was occupied by CHDR in May 1995. The building was a revolutionary design by the Delft firm CEPEZED, and was so successful that three buildings in a row were all designed by this firm (for DuPont Octoplus and CHDR). The move was historic because at this point CHDR started to create its own space and increasingly became responsible for its own operations.

Just before the move, the senior staff was also expanded with the addition of Joop van Gerven, who had just finished his neurology specialisation. Joop did his PhD in diabetes research before his neurology training and he rapidly took over the CNS research at CHDR, establishing a line of research that remains a hallmark of the organisation.

Advanced drug research is an art. To inspire staff and visitors, this artwork by textile artist Ella Koopman received a prominent place in the new building.

The show must go on, sometimes. The foundations for the expansion of the building are being built quite close to the rooms where sensitive measurements on the central nervous system take place. Our data show an amazing robustness of both our subjects and staff members.

Building in the 21st-century sometimes has an aesthetic of its own, especially in retrospect, and preferably without the soundtrack.

Thinking outside the box, the hard way: what if someone smashes the walls of your working space? CHDR staff have the flexibility to deal with daily diversions like these.

Adam Cohen had been appointed as full Professor of Clinical Pharmacology in 1993 and CHDR entered its new premises with plans for a big expansion in scientific output. At the same time, our involvement in education grew, teaching pharmacology and pharmacotherapy, and as CHDR needed a growing turnover from contracts, there also was a need for a much more sophisticated quality system.

All of these activities were undertaken at the same time – probably inspired by the dynamism resulting from a changed environment. The quality system received a Good Clinical Practice (GCP) certification by the Netherlands Health Inspectorate and CHDR appointed Ria Kroon as its first Quality Assurance manager. The education program for medical students was expanded and the first steps towards the Teaching Resource Centre were made, as will be explained in a later chapter in this book.

The research staff and the nursing staff were expanded and the new custom built research unit attracted a considerable amount of the specialised work that was the intended niche of CHDR. This also resulted in an increasing stream of PhD theses.

BUILDING AGAIN

The design of the CHDR building allowed for a potential expansion by 50%. As business was expanding, this expansion was realised in 2003. Those who were present at the time may remember that this operation was a bit challenging at times.

The elongation of he building was built quite close to the existing part. The builders of course said this would not be much of a problem but doing a CNS experiment while half a meter outside your window a pile is being driven 20m into the ground may be at odds with your expectations concerning a quiet environment.

The final attachment required removal of the partition and Aernout van Haarst, who was our operational manager at the time recalls that he was going about his business when a angular grinder started to slice through his office wall. Somehow CHDR battled through and once the increased capacity it was realised, it it was really useful in the larger studies that were increasingly required.

TOWARDS CHDR2

By 2005 the trauma of the refurbishment was over and the CHDR started to expand the business further. Teaching activities were professionalised by the arrival of Kari Franson, a US trained clinical pharmacist who took the pharmacology teaching in Leiden to new levels by introducing computer assisted teaching (culminating in the TRC website) and by redesigning the basis pharmacology course. She defended a thesis about this in 2008. The number of research scientists expanded to the point that more staff was required to guarantee supervision. An expansion of the staff also helped to provide the clients of CHDR with better and more personal service. Justin Hay, Matthijs Moerland and Ingrid de Visser were appointed as senior project leaders.

CHDR became one of the larger training sites for clinical pharmacology board certification and a very popular site for elective students. When Kari Franson left, Robert Rissmann joined as education manager.

The CNS field expanded to the level that a new research director was required and Geert Jan Groeneveld joined in 2009. Geert Jan was trained as a neurologist. He had worked for Genzyme and wanted to return to a more scientific job. CHDR was at the time already discussing collaboration with the Amsterdam Vumc (Free University Medical Centre) - initially because of its PET capacity. Geert Jan developed this collaboration further with the opening of dedicated beds in the hospital for joined work and started a research line in degenerative neurological diseases (the subject of his PhD thesis) and pain research (with Justin Hay).

The final addition to the work was by a collaborative agreement with the Netherlands Organisation for Applied Research (TNO) in the field of food research. Pierre Peeters, was head of Clinical Pharmacology at Organon and subsequently Schering Plough and then Merck. He managed this extraordinary amount of job hopping by staying in the same place while his company was taken over two times. He decided not to wait for the third take-over and joined CHDR in 2011 to do general management and expand the nutrition research.

BUILDING AGAIN

Around 2007 it became clear that the building would again be too small and insufficient to handle larger studies with longer in-house periods that the market required.

Joop van Gerven and Adam Cohen recall what happened as they were discussing the future one Monday morning
‘We were sitting in Adam’s room that overlooked a neighbouring green field and wondering how we were going to deal with the future when we suddenly realised we had to enlarge the building quite a bit and needed the adjoining field. Adam called the Leiden City Hall and put a claim on the land. We were quite lucky because a property developer tried to claim it just days after us’

This hapless hedgehog almost fell victim to our ruthless expansion, as it attempted to hibernate on the building location. Luckily, it was rescued in time.

This is not our corporate fitness studio, but one of the many tests employed in cardiovascular drug research. To the left, [functie] Toos Beekman.

Informing subjects about clinical experiments is of course an important part of our procedure. Here, Richard Faay informs a group of students.

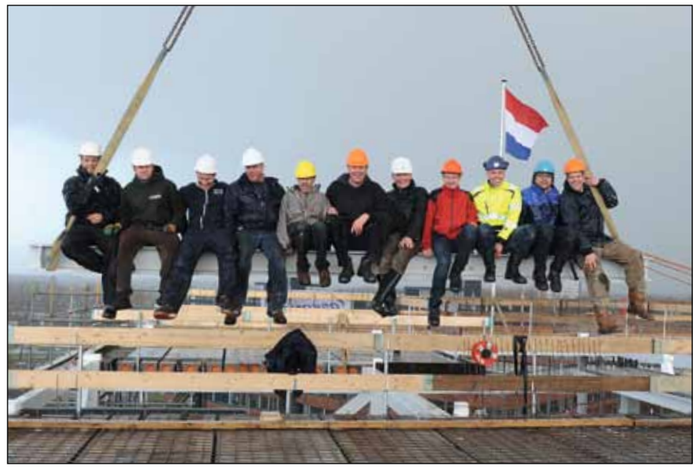
A historical moment: the signing of the land sale for the new building. In the middle, Adam Cohen. To the right, Robert Strijk of the Leiden City Council.

The next step towards our new building: groundbreaking ceremony. From left to right: Martijn van der Mandele (chairman of the Board of Advisors of CHDR), Henri Lenferink (mayor of the city of Leiden), Paul van der Heijden (then rector magnificus of Leiden University) and Adam Cohen (CEO of CHDR – please notice the ancient Roman helmet he wears, in honour of his firm defence of the Latin language as lingua franca at Leiden University).

Joost Visser was the main supervisor of the building process. Thanks to his sharp eye for details and his perpetual good mood all the usual hurdles were taken without unnecessary gastric ulcers and/or temper tantrums.

Almost a postcard: the people of CHDR in the building pit, looking into the future.

Everything proceeded rather rapidly. In the eyes of irregular visitors to the Leiden Bioscience Park, the new building emerged almost overnight.



And then, the last beams were put in place. At the topping out ceremony, builders and CHDR people enjoyed a good view and a fresh splash of rain. Candidate compounds which proved effective against acrophobia contributed to the festive atmosphere.

Almost ready to move: CHDR employees take a look at the new building.

Okay, next time we'll build a pyramid.

From then on plans were made. There were several setbacks as the size of the plot did not allow the required amount of parking space. Underground parking is expensive in the Netherlands as one has to build under the water level but the city of Leiden helped by providing facilities. At this time the city was already aware of the the Science Park as an important asset and CHDR received quite a bit of help in developing the site. The building was again designed by CEPEZED and the architectural and technical aspects are described in another chapter of this book.

On June 21st 2011 Paul van der Heiden, Rector Magnificus of Leiden University and Henri Lenferink, Mayor of Leiden jointly drove in the first 25m deep pile to support the current building. CHDR moved into this new building in February 2013. Just before that moment the CHDR family was shocked by the sudden death of Frank Stap, the financial director of CHDR who had been so important in guaranteeing the financial basis for this move.

TOWARDS THE FUTURE

In the next twenty years, the development of new medicines will again be highly exciting, and probably more so than it was in the last two decades. We are already seeing the benefits from the explosion of biological knowledge through genomics, expanding our understanding of disease mechanisms. It is generally accepted that future drug development requires innovation in the process of development itself and that the traditional research organisations will not be able to deal with these requirements for change. Additionally, the time of development of single medicines is coming to an end. We are already seeing combinations of drugs, surgery, nutrition and medical devices.

CHDR believes that in the future drug development will take place in goal-oriented clusters of scientists and supporting staff that will form and dissociate when needed.

It is clearly not buildings that have kept CHDR together over all these years. The open, professional and mutually supportive culture that the small team developed in the ramshackle building 50a of the old Leiden university Hospital has survived over a quarter of a century and can still be sensed today. But all of this would never have been possible without the vision of Douwe Breimer in 1986 and the extraordinary strategic financing of those days.

Frank Stap (1946-2013) was the first financial director of CHDR. He joined the foundation in 2005 and contributed greatly in the professionalisation of the financial and administrative part of our organisation. As such, he contributed to our commercial success and our stability. As a colleague and personal friend of many CHDR staff members, he contributed to our team. On March 1st 2013, he passed away, just shortly before he would have moved his desk to the new building. He will be missed.

The NeuroCart

The history of the measurement of CNS effects at CHDR

The story of the NeuroCart began in the Wellcome Research Laboratories in Beckenham, UK. Adam Cohen started his career as a clinical pharmacologist in the clinical research unit in 1981, and remembers how this all came about.

'The research labs of Wellcome, in a leafy suburb of London, were housed in a sprawl of buildings around an old country house called the Mansion where the management resided. Wellcome operated at the highest scientific level, and four of its scientists received Nobel prizes while I was there (John Vane, Jim Black, George Hitchins, and Gertrude Ellion). The human experiments took place in a separate clinical research unit where all of the first drug administrations to humans and other experiments were conducted. When I started, these experiments were performed without an ethics committee; we received permission from one of the directors to conduct the trials.'

VIGILANCE

The CNS research was headed by Tony Peck. Tony was a general internist who was also a trained physiologist (in the lab of Samson Wright at the Middlesex Hospital Medical School). Tony got involved in research on antidepressants, and had done work to show that the pharmacodynamics of a potential Wellcome antidepressant, benzylpiperazine, was very much like amphetamine and just as addictive. This meant the end of the compound as a useful drug. It did, however, result in the establishment of a facility to measure stimulatory effects of medicines at Wellcome. The test used for this measurement was the Wilkinson vigilance test. This test originated from work done at the Cambridge Applied Psychology unit during the Second World War to test whether amphetamines would improve the ability of sonar operators keeping watch to detect submarines, and required the subjects to detect bleeps over white noise that were slightly shorter than regular bleeps. The test took a full hour and was sensitive (and not very popular with the subjects, as it was designed to be extremely boring).

'When I joined, Wellcome had gone through a slow period of innovation after the extraordinary wave of new compounds found through the work of Ellion and Hitchins, which included azathioprine, 5-mercaptopurine, allopurinol, trimethoprim-sulphamethoxazole, and others. The first new compound was acrivastine, a non-sedating antihistamine. This required us to show the absence of a CNS effect, which had never been done before. Tony, who had validated this previously, had already developed sensitive tests and equipment, so we were able to use the visual analogue scale of Bond and Malcolm Lader (still part of the NeuroCart today), as well as the Wilkinson vigilance test. We also measured dermal antihistamine effects –such pharmacodynamic and challenge tests in comparison with a positive control were entirely normal at Wellcome in 1981. These tests enabled us to establish the potential dose range for the drug very quickly.'

STUDYING EFFECTS IN EARLY PHASE

'Such studies have since become rare, and at CHDR we still spend a lot of our time convincing companies that it is really useful to study drug effects during the first-in-human study, and not at all revolutionary. Strangely enough, now a majority of people developing medicines appear to think that such studies can only look at tolerability and safety.'

'A number of things became clear. The Wilkinson test was not well adapted to compounds with a short half-life, because the duration of the test was too long. Younger readers may be surprised about this, but in 1981 the measurement of drugs in biological fluids was just becoming standard, and the pharmacokinetics of many older medicines were still unknown.'

'I learned more about this because of my continuing contact with Douwe Breimer in Leiden, who had taught me pharmacology and was one of the pioneers of pharmacokinetics. I occasionally went to Leiden to present what I was doing in England, and Douwe convinced me that pharmacokinetics and dynamics should be measured together. In Wellcome at the time, we felt that it was unethical to take blood samples from subjects being treated with placebo, and we were concerned that the blood sampling might disturb the pharmacodynamic measurements. This protocol needed to be changed, and it was.'

LAMOTRIGINE

'At the same time, shorter and more sensitive tests were required to couple effects of drugs with their concentrations. As we were develop-

A body sway test

ing acrivastine, Tony Peck as the clinician and Alasdair Miller as the pharmacologist, along with the chemist Dave Sawyer, were advanced in the development of BW430C, now known as lamotrigine (Lamictal). This antiepileptic drug was supposed to be more selective (and cause fewer side effects) than phenytoin.'

The main side effects of phenytoin involve the eyes and cerebellar motor control. The required instrument to test for the latter side effect was the adaptive tracker, a test developed in the Royal Air Force Aviation Medicine unit in Farnborough by Group Captain Tony Nicholson. It was a test of hand-eye coordination based on an earlier instrument called the pursuit rotor, which consisted of nothing more than a record turntable with a contact spot. The subject had to try to touch this spot with a stylus and the amount of contact was recorded. The adaptive tracker was a circle and a spot on a large oscilloscope. The spot was moved by a joystick, and if the spot was moved inside the circle then the speed of the movement of the circle increased. In this way the test adapted, and the speed that the movement of the circle reached was the performance. If hand-eye coordination were impaired, then the circle speed reached would be lower. For the first time, such a setup required considerable computing power, which of course was unavailable at the time. Alan Strutt and Kevin Hobbs at the Wellcome's electronics lab were able to supply the necessary computing power using an Apple II PC – with the program on one 64-Kb (not Mb!) drive and the data on another! The simple graphical picture could only be generated in an analogue fashion on an oscilloscope rather than a monitor. This test, in several updated versions, is also still part of the current test battery, 30 years later.

'The clinical pharmacologist at St. Bartholomew's hospital at the time, Alan Richens, had developed a test of the speed and accuracy of eye movements. It appeared that this measurement might be particularly useful during the development of an antiepileptic drug, as phenytoin produced double vision as a side effect. Additionally, the test was short and required little subject cooperation or training. The amount of computer power required was at the edge of what personal computers could do at the time, but we managed to hook up the Apple II to an enormous Grass bioelectric EEG amplifier, digitise the signals, operate a spot on the oscilloscope for the subjects to watch, and record their eye movements by electrooculography. The test had to be evaluated overnight, as the Apple II took about an hour to work through the data from a single 5-minute experiment. The fact that we did manage to get significant results from this test is a tribute to the fantastic technical support available at Wellcome.'

ATAXIMETER

When lamotrigine was developed and further testing of acivastine continued, it became clear that a single test would be insufficient to study the CNS effects of new medicines, and the set of tests (subjective effects measured by visual analogue scales, eye movements, and adaptive tracking) had already become a standard battery.

'Because postural instability was another well-known side effect of phenytoin, we added the Wright Codoc Ataximeter, a very simple instrument that recorded the amount of body movement of a subject standing upright with eyes closed.

These tests were able, again in the first studies of lamotrigine in humans, to indicate that the adverse events of lamotrigine would be much reduced compared with phenytoin, an antiepileptic drug with a similar mechanism of action. This advantage was maintained throughout the subsequent life of Lamictal, which became a >$1 billion product.'

'Around 1986, computing possibilities had expanded and we began a collaboration with the high-tech electronics firm Cambridge Electronic Design, which had been established by Greg Smith. CED interfaces have been a part of CNS measurement ever since, and these instruments were so advanced at the time of their original adoption that they are still usable today. CED interfaces also made it possible to analyse EEG signals, and we commissioned this work just before CHDR started in 1987.'

DEMONSTRATING SEDATION

'When I started in Leiden in 1987, we had a single set of this measurement equipment to study drug effects. Our first research fellow, now applying this in a more academic environment, was Fred van Steveninck (now intensivist). He established the sensitivity of the tests for benzodiazepines and studied several new and old drugs to evaluate pharmacokinetic-dynamic relationships for the first time. The partial benzodiazepine agonist bretazenil was tested at CHDR, and the company developing it was convinced that it should be a non-sedating anti-anxiety drug. Earlier studies in healthy volunteers (performed without our sensitive equipment) had demonstrated absolutely no sedation. Fred easily showed that the drug was more sedating than 10 mg diazepam. This was near the end of the prehistory of CNS measurement at CHDR, and we did not know how much was still to come.'

'All of the work that I have discussed so far was done in the original CHDR, and in 1994 Joop van Gerven joined CHDR. Joop was a board-certified neurologist with experience in neurophysiology and drug research. Soon after he took over the CNS research from me (Adam Cohen), Joop was approached to set up a first-in-human study, which included the repeated performance of CNS measurements, as well as the administration of two new benzodiazepines in the same study. The aim was to select the compound with the shortest onset and duration of action, with an application as short-lasting sedation during outpatient surgery, imaging, and other elective procedures. The sponsor was quite advanced in considering the use of CNS pharmacodynamics and concentration-effect relationships for the selection of drugs and dosages. However, most of the team considered first-in-human-studies a commodity, with a large emphasis on rapid timelines and process efficiency. The study design required that every day of the week for 4 weeks, healthy subjects would receive an ascending dose of one of the two compounds, or a positive control, or placebo; and that eye movements, EEG, and visual analogue scales were measured frequently. This approach required not only a doubling of the available equipment (some of which was still hand-crafted), but also a doubling of the speed with which data were processed and analysed. Such changes also occurred with other projects, which fuelled considerable debate among research and nursing staff about the future of CHDR. But the clear results of this complex study also provided confidence that the CNS tests would be very useful for drug development decisions if their performance and analysis could be streamlined. Rik Schoemaker performed the statistics and PK/PD (pharmacokinetic/pharmacodynamic) analyses at CHDR, and he started to improve the eye movement and EEG scripts to speed up post-processing and the analysis of measurements. These efforts continue today.'

DIFFERENT TESTS FOR DIFFERENT TYPES OF DRUGS?

Very soon, a plan arose to create a library of CNS effects for a range of pharmacological compounds. This library could be used to benchmark new compounds with specific mechanisms of action. Unfortunately, it was impossible at the time (late 1990s) to find public funds or pharmaceutical industries (or combinations) willing to sponsor the construction of such a database with a dedicated research programme. Nonetheless, ever more studies were performed at CHDR. Sponsors offered an increasing variety of drugs, such as centrally acting analgesics, antihypertensives, and compounds with innovative pharmacological mechanisms. Usually, these studies were designed to obtain information about the therapeutic window or the side effect profiles of these investigative drugs, and their therapeutic congeners were often used as positive controls. Sometimes the methods showed effects, and in other cases they did not. Therefore, despite the gradual accumulation of data, this hodgepodge of drugs and mechanisms allowed very little integration of data regarding the CNS tests that were employed at CHDR. Nonetheless, efforts continued to create a conceptual framework for the value of CNS measurements in drug development.

Two researchers contributed substantially to this integration. Jeroen van der Post gathered the early CHDR experience from widely different drug studies. He argued that CNS tests might serve different purposes, and can be used to quantify different aspects of drug action, such as blood-brain-barrier penetration, pharmacological activity, desirable or inadvertent CNS functions, or pseudo-therapeutic effects on disease models. His work strengthened the awareness that in drug development programmes, tests should actually be chosen with a specific aim. In some cases, a test can prove that a certain drug dose achieves the intended pharmacological effect; in others, the test objective is more to predict or compare a drug's potential side effects or provide indications for functional benefit; and in yet other instances, a disease model may help to provide an early indication of therapeutic efficacy. To a large extent, this variability reflected the rather variable expectations and interpretations of early sponsor studies with the CNS tests. However, Jeroen also performed some dedicated studies to search for new methodologies with a very specific objective, which increasingly also included neurophysiological and neuropsychological testing. This framework was used by Saco de Visser to develop his model of question-based development.

CLASS SPECIFICITY IN SYSTEMATIC REVIEWS

Saco also completed the first three of a series of systematic literature reviews, to investigate the sensitivity of tests to a particular class of drug in healthy volunteers. To integrate and compare the results of the tremendous variety of tests across hundreds of studies, a novel semi-quantitative data reduction technique was developed that was characterised by the first journal as 'a brutally simple form of meta-analysis'. Currently, similar systematic reviews have been published on most major drug classes, and the ninth review in this line is close to submission. Each review has identified tests that are very sensitive to a certain drug class, but not to other classes (e.g., prolactin is sensitive to dopamine antagonists, and saccadic eye movements are sensitive to benzodiazepines).

The reviews also showed that there are more tests than publications, that 90% of the tests were used only once or twice, and that most psychological tests only demonstrated significant drug effects in 40-60% of studies (and by extension failed to show effects in the rest.) Whatever these outcomes tell us about psychological testing in drug development, they also increased the awareness that CNS effects can be highly specific to a drug class, and that specificity is particularly shown by combinations of effects. It appeared, for instance, that anticholinergics and benzodiazepines cause fairly similar impairments of eye movements, postural stability, adaptive tracking, and visual analogue scales; however, the EEG effects of the two classes are quite different. Thus, drugs are best characterised by profiles across a range of CNS effects, rather than by a small number of tests or single tests.

The systematic literature reviews also demonstrated that the old Wellcome tests were usually among the most sensitive methods, which provided confidence in both the test battery and in the methods used to make the reviews. On the other hand, the reviews stressed the fact that drugs can affect a number of functional domains of the CNS, which were not all captured by the tests that were routinely used by CHDR.

NEUROPSYCHOLOGY

Certain drug classes can specifically affect functions such as impulsivity and memory, so there was certainly a need for specific neuropsychological tests. In the 1980s and early 1990s, the FePsy programme ('The Iron Psyche') was occasionally used for these purposes. This test battery was adopted from the Dutch epilepsy centre SEIN, where it had been mainly developed to measure the cognitive effects of antiepileptic drugs. However, FePsy was inflexible and worked in an antedated DOS software environment. Therefore, the ePrime system for neuropsychological test development was added to the armamentarium. This open system allowed us to adopt neuropsychological tests from other researchers, and to develop our own tests if required.

'MEASUREMENT ASSISTANTS'

Assisted by these rational evaluations of the literature and by the public exposure of presentations and publications, the CHDR test battery gradually gained wider acceptance among sponsors, and the number of studies increased steadily. Around the turn of the century, CHDR started to recruit and train students to perform the growing number of measurements. In the past decade, the number of 'measurement assistants' has expanded to a pool of around 80 persons. Many measurement assistants maintained connections with CHDR throughout their academic education, and several joined CHDR after graduation to be trained as clinical pharmacologists or project leaders. In the past decade, measurement assistants have become an essential link between CHDR and the student community.

REFERENCE VALUES

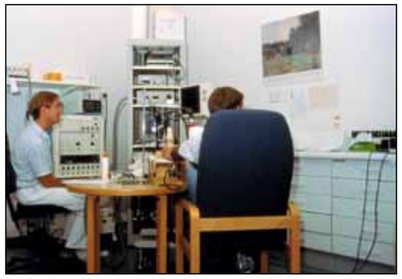
The results of the sponsor studies were used to further investigate the predictive value of the CNS tests. After 2005, enough studies had been performed to allow formal meta-analyses on all raw data in the CHDR database. Formal meta-analysis of our data enabled us to define reference values for healthy subjects for the CNS measurements, and to calculate 'minimal detectable effect sizes' for a number of classic psychoactive agents. The availability of this measure strengthened the statistical rigor of our study proposals. Justin Hay (who joined the CNS team as a senior scientist) also performed two meta-analyses on the profiles of the various drug classes that CHDR had examined in the previous 20-odd years. Justin's meta-analyses clearly confirmed that drug classes had unique effect profiles that could be used to characterise novel compounds. This concept was strongly supported by the sudden popularity of ∞1-selective GABA-A-agonists, which were shown by Sanne de Haas to have distinctly different effect profiles compared with non-selective benzodiazepines. These functional characteristics correlated well with the ∞1-selectivity of these agents. The direct comparison with a benzodiazepine also correctly identified the anxiolytic dose for an 1-selective GABA-A-agonist that was tested in a clinical trial.

PREDICTING EFFECTIVE DOSES

The capability of CHDR's multidimensional CNS test battery to demonstrate subtle pharmacological modifications and predict therapeutically active drug levels greatly supported the approach that CHDR was offering to clients. Over the years, a number of drugs that were initially studied with the NeuroCart have since been investigated in clinical trials. In most cases, pharmacological activity using the NeuroCart also reliably predicted effective doses in these clinical trials. Such predictions were particularly valid for drugs with novel mechanisms of action, such as the sleep-inducing doses of the first orexin antagonist, the antipsychotic dose range of a new fast-dissociating D2-antagonist, the anxiolytic dosages of a partially subtype-selective GABA-A-agonist, and the weight-reducing doses of a cannabinoid receptor antagonist.

THE NEUROCART IS BORN...

Before 2005, studies were still performed with a limited number of setups, which basically consisted of a screen and a computer connected to an analogue-digital converter with several input and output devices. This typical academic construction was rather inflexible, which caused planning problems with other non-CNS studies that competed for the same testing rooms. The setup also started to get out of tune with the increasing demands of quality systems and logistics.
In 2006, Nina Pander, an industrial design student, was given the assignment to develop an ergonomic integrated system, which was soon baptised The NeuroCart because it was movable. The system could therefore also be used on other sites, such as allied hospital departments. The expansion of the number of NeuroCarts called for a more industrial approach to the measurements. Operator interfaces were simplified, output systems were semi-automated, and checks were built in to improve quality and reliability. These changes further increased the capacity of CHDR to perform intensive CNS studies just as quickly as any other traditional phase I study. The innovation of The NeuroCart contributed significantly to the accelerated growth of CHDR during this period, which led to the decision to start building a new facility in 2006.



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A Forearm blodd flow measurements in the measurement room in CHDR1. Originally one of the cold rooms of the hospital pharmacy

B EEG

C Monique Pieters uses the CNS measurement room as an office as space becomes limited just before the move to the new building

D Eye movement measurements – no sign of a neat neurocart yet...

E Jean van Griensven on the old adaptive tracker. The screen is an oscilloscope so entirely analogue!

F Nina Pander designed the new neurocart as an elective student in industrial design from Delft University

G Digital version of the tracker a long way from the original in the Royal Airforce Aviation Medicine unit in Farnborough.

...AND GETS A SISTER: THE PAINCART

The success of the NeuroCart provided inspiration for new initiatives. As a neurologist with a background in diabetes and oncology, Joop had always had an interest in pain. Justin's PhD was on pain, and he was eager to set up a measurement battery for pain with the same basic structure as the NeuroCart: flexible, multidimensional, semi-automated, and validated for drug development purposes. In 2009, Geert Jan Groeneveld came over from Genzyme, to join CHDR's CNS group as a neurologist with an emphasis on neurology and pain. The lessons that had been learned from the development of the NeuroCart assisted in the maturation of The PainCart. It was clear, for instance, that test validation mainly occurs 'by experience', and the industry is less willing to sponsor studies that use poorly validated methods. Therefore, to build confidence in The PainCart, CHDR has continually invested actively in the development of the system, including active collaborations and self-funded studies with analgesics to demonstrate its usefulness. Fortunately, the interest of pharmaceutical industries in analgesia started to rise, and pain tests had much greater face validity for analgesic effects, than (for example) saccadic eye movements for anxiolytic drug effects. Currently, analgesic studies using The PainCart contribute significantly to the growth of CHDR's CNS activities.

CNS RESEARCH IN TIMES OF CRISIS...

In 2011, Glaxo SmithKline publically announced its withdrawal from psychiatric drug development, which was considered too risky in view of the economic crisis. This decision was followed by similar decisions by most other major pharmaceutical businesses, and had a huge impact on many smaller companies, which relied on the large ones to support their development programmes. This decision also caused the bankruptcy of several contract research organisations that specialised in CNS research. Academic researchers organised conferences, and Joop and Adam published an editorial in the *British Journal of Clinical Pharmacology* to describe how the tide could be turned by new psychopharmacologic approaches. These developments also had consequences for The NeuroCart, which had been most extensively validated with psychoactive drugs that were now much less in demand. The slow-down was used to further improve The NeuroCart by bringing the system into compliance with US Food and Drug Administration quality standards, updating the computer systems, and modernising the design of the cart and of some of the measurement systems. In addition, new possibilities were created to distribute The NeuroCart more widely. To this end, a transportable flight-case version was built, a system for remote 'on-line' operation and data processing of NeuroCart tests was set up, and a business model was created to provide The NeuroCart as a service to other companies and researchers across the world. These activities were intended not just to reach more potential customers with The NeuroCart, but also to expand the use of The NeuroCart to patient studies, which in turn will contribute to further validation of the system in more advanced drug development phases. Very soon, the first NeuroCarts will be implemented in the United States and Romania.

... AND BOOMING BUSINESS

Meanwhile, it seems that psychopharmacology has not vanished at all. Instead, it appears to have resurfaced more vigorously during the past year, with a greater interest in innovative approaches, and with the intent to adopt more rational approaches to the development of drugs for CNS indications. As a result, the demand for The NeuroCart is greater than ever. This could not have come at a better time for CHDR, and holds great promise for the future of our new building.

LONG TIMELINES

Thus far, the development of what is now The NeuroCart has progressed for well over a quarter of a century, and is perhaps an example of how long the time horizon must be to achieve success in biomarker development. It takes a long time to build enough confidence in a system to use its data as a basis for important decisions – much longer than we would have thought in the beginning, and much longer than would seem commercially sensible if one were to be interested only in yearly cash and profit growth. As is so often, but so rarely stated, there is more. In many ways, we share the commitment of our clients to provide patients with good drugs. Creating good drugs relies on good methods, and that is CHDR's contribution.

Trusting each other enough to share doubts

TO CREATE SHARED VALUE AND KEEP DEVELOPING IN TIMES OF CHANGE, IT IS VERY IMPORTANT TO INVEST IN LASTING RELATIONS WITH OTHERS WHO CAN BE TRUSTED AND WHO HAVE AN OPEN EYE FOR THE DEVELOPMENTS IN THEIR FIELD. AN EXCELLENT EXAMPLE IS THE LONG-LASTING COLLABORATION BETWEEN CHDR AND PROFESSOR KEES KLUFT, DIRECTOR OF GBS LEIDEN. AFTER MANY YEARS OF COLLABORATION, HIS COMPANY NOW IS EVEN LOCATED IN THE NEW CHDR BUILDING. 'A CERTAIN PHENOTYPE OF PEOPLE WHO DARE TO QUESTION CERTAINTIES SHOULD STICK TOGETHER. WE TRUST EACH OTHER ENOUGH TO SHARE OUR DOUBTS, AND THAT'S OFTEN A GREAT STARTING POINT'.

Contacts between Kees Kluft and CHDR director Adam Cohen started long before either of them even thought of starting a company, when they were both at the beginning of their careers. Cohen remembers: 'In 1985, when I was back at Wellcome again, I was put in charge of the first biotech endeavour, which was centred around t-PA, tissue-type plasminogen activator. It was not unusual at Wellcome to be given such an important project without having any specific knowledge or experience. Our first work question was: t-PA, what was that again? So I looked it up and it turned out to be a protein that could trigger the fibrinolysis, re-establishing the bloodstream after a myocardial infarction. Reading up on this promising protein, one name repeatedly popped up in the literature: Kees Kluft. At the time, he was employed by the TNO Gaubius Institute in my hometown Leiden where he and his colleagues (notably Dick Rijken) were among the first to purify tPA. So I decided to write him, if only to make it easier to declare my trips home. In my first letter, I asked him what parameters we should check in our clinical studies with t-PA. I promptly received a letter back, with three pages filled with assays we should perform in our patients. 'Isn't that a bit much?', my boss asked. But we did decide to collaborate with him in our first clinical trials with t-PA.'

Kluft: 'Yes, I remember how we tried to recruit cardiologists for those first groundbreaking clinical trials. One of them was professor Attilio Maseri from the Royal Postgraduate Medical School of London University and head of the cardiology department at Hammersmith Hospital. He was a leading expert on myocardial infarction and he was convinced that the main cause of such infarction was coronary spasm. That was the leading paradigm at the time. Of course, if a spasm was the main event, fibrinolysis would not do much good.

So Adam asked me to help him to change his mind and consider the possibility that t-PA might help to limit the damage after myocardial infarction. We did, the trial went successful and it was the beginning of another long-term collaboration. When Maseri went back to Italy in 1991, I assisted him in establishing a laboratory in Rome and I regularly travelled down to Italy. All this thanks to Adam who put me in touch with Maseri in the first place.' Cohen: 'Yes, sometimes one can play the role of catalyst; I always love it when it works, even if I do not benefit directly.'

CANDY STORE

Nowadays, at CHDR, Kluft's closest collaborator is Koos Burggraaf, professor of translational drug development at Leiden University and Research Director cardiovascular system and Metabolism at CHDR. 'We both believe in providing intelligent services, creating something extra. Of course, we want to meet the needs of our clients, but we also want to contribute to the development of knowledge in the development of people. We have quite a track record in coaching Ph.D. Students. You could call that another example of shared value. And now, we are lucky to be have enthousiastic young colleagues who want to take up the torch: Mathijs Moerland in my team and Karen Malone in Kees' company.'

Kluft: 'Developing yourself is also important, unless you want to become a one trick pony, stuck in your comfort zone. That is why it's nice to be close to other people like Adam and Koos, who dare to question your assumptions and who do not mind if you undermine their pet theory. For me, CHDR is quite a candy store, where they always study new mechanisms and new drugs from an innovative perspective on clinical problems. I'm actually a pensioner, so after all these years I finally have the time and the freedom to ponder scientific questions, to be a scientist. And I must say, I feel like Livingston in Africa almost everyday.'

Despite his Italian connections, Kluft has always stayed in the Leiden region. Gaubius Laboratory was a breeding ground of innovative cardiovascular research, collaborating closely with scientists at universities in the Netherlands and abroad. In the early 1990s, the laboratory moved to the Bioscience Park, in fact close to the current location of CHDR. A change of policy of the TNO organisation of which Gaubius was a part led to a radical reorganisation. In 2007 Kluft and his colleagues decided to start their own company, marketing their knowledge of biomarkers. The time was right: 'Everyone in drug development was suddenly talking about biomarkers. That's what we were good at, and we have developed our expertise since then. Our scope is broader than CHDR's, because we also measure biomarkers in large-scale clinical trials. But we like to be involved in the early stages – those studies help to refine our knowledge of the pathophysiology.'

INFLAMMATION

Burggraaf and Kluft explain how the paradigm in cardiovascular research has been shifting over the years. Some people focus on coagulation and fibrinolysis, others on cholesterol and fatty acids or the inflammatory response. Most research will be 'wet' biology, using serum concentrations as the main parameters. Sometimes functional measurements and/or imaging is used to obtain additional information. But the primary pathophysiology is localised in the vessel wall, in the endothelium and the underlying layers. That is where atherosclerosis manifests itself, that is where the complications of diabetes will develop. The endothelium holds the key to high blood pressure, pathological blood clotting and other dangerous processes. And what characterises a diseased vessel wall? Inflammation. Koos Burggraaf: 'We talk about a form of inflammation that we have almost overlooked for decades. You see, on one side of the spectrum you have the acute infection and the immune response to that I think it's fair to say that biomedical science has a good grasp on what's happening there. On the other hand there is the autoimmune phenotype. That's a lot more complicated to explain and understand, but clinically, we know what we are talking about. The kind of cellular inflammation that is the focus of our research is somewhere in between these two extremes. Most of the time it stays under the radar, as a subclinical process, until the patient develops symptoms. To study it, we can make use of the repertoire of tools developed by scientists studying infectious diseases and autoimmune disorders. That allows us to study specific compounds that promise to interfere with these inflammatory pathways. One major obstacle is of course that you cannot trigger severe inflammations in healthy volunteers. But we have found a way to overcome that.'

'Yes', Kluft jumps in eagerly, 'We do not have to make the volunteer sick, we can make his blood sick in the laboratory. Studying the inflammatory response in peripheral blood can give you with first indication of an intervention might work.'

Such laboratory studies however can be a source of confusion without knowledge of the clinical syndromes and their pathophysiology. As Burggraaf puts it: 'Good drug research implies good disease research. You must always be careful for pitfalls; similar phenotypes can be caused by different pathophysiological pathways.' Kluft: 'A drug can be a very useful tool to understand the process. That's why I referred to CHDR as my candy store.'

Teaching doctors to use medicines 2.0

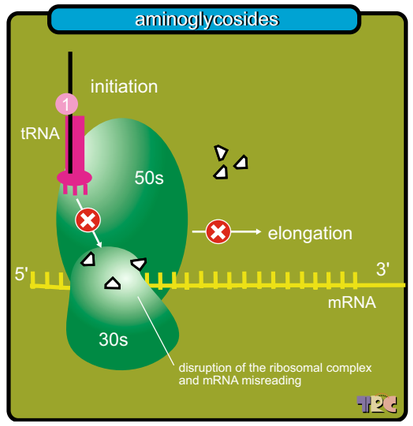
EDUCATION IS ONE OF THE MAJOR WAYS TO SHARE VALUE. CHDR TAKES ITS EDUCATIONAL OBLIGATIONS REALLY SERIOUSLY, FROM THE TEACHING OF STUDENTS TO STUDENTS WHO WANT TO KNOW MORE ABOUT THE CLINICAL RESEARCH PRACTICE AND PHYSICIANS WHO WANT TO SPECIALISE IN CLINICAL PHARMACOLOGY. AN OVERVIEW OF DIFFERENT ACTIVITIES AND, OF COURSE, THE POPULAR ONLINE TEACHING RESOURCE CENTRE.

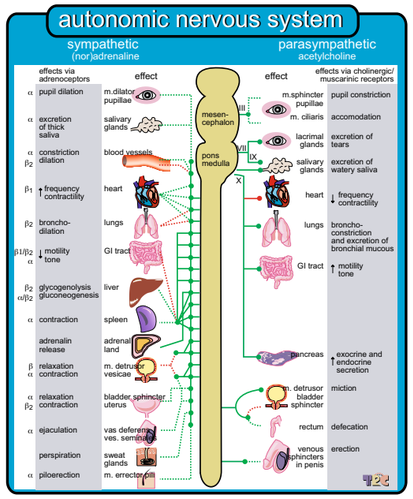
Pharmacology is of course a recurrent theme in (bio-) medical and (bio-) pharmaceutical education. It is highly integrated in all the different clinical subjects, but the students also need understanding of the basic principles. In medicine pharmacology is taught at the end of year one with an intense course dedicated to the basic principles: pharmacokinetics and pharmacodynamics including clinically relevant examples. Pharmacology and pharmacotherapy classes later on in the curriculum build on that repertoire to train students to make a rational choice of the drug and the dose thereof [1]. For this purpose the six-step methodology, a concept-based learning strategy to achieve a structured therapeutic plan, has been introduced in the Dutch medicine curricula – having CHDR as one of the facilitators for the implementation[1-2]. Educational tools for rational prescribing involve understanding of basic and clinical pharmacological principles, practicing to write 6STEP therapeutic plans, learning from feedback sessions on these plans and actively obtaining up to date information on drugs and therapeutic standards from online resources – all of which is being facilitated at CHDR.

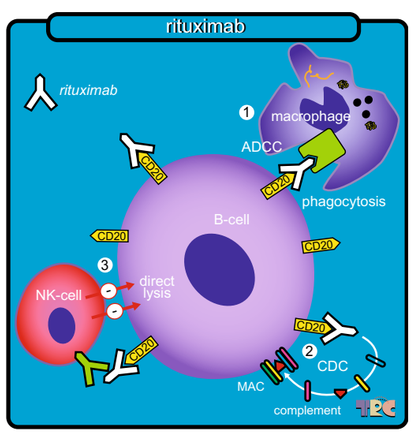
PHARMACOLOGY E-REPOSITORY

To make studying pharmacology more attractive and more easily accessible, we developed a special online database, called the Teaching Resource Centre (TRC). TRC is like an e-book using consistently the same symbols and terminology. It is free to use for anyone and is personalised, so you can see what subjects you already studied. Kari Franson, who invested a lot of time in developing TRC, has shown that there is a strong correlation between the time people spend in TRC and the results they get in the exams[4].

A quick review of TRC (http://coo.lumc.nl/trc/) shows how it builds on basic concepts, connecting them with different clinical subjects and the toolkit used to support choices in pharmacotherapy. TRC trains students in using this six step approach during the entire medical curriculum. Whenever they







need additional information about drugs, they find links to the Dutch Formularium (Farmacotherapeutisch Kompas) and the system was complemented by multiple choice questions with feed back. All this led to widespread use by students worldwide and formal use by a number of universities. The most recent development are apps for iPad and iPhone that now bring pharmacological information to the classroom and the bedside.

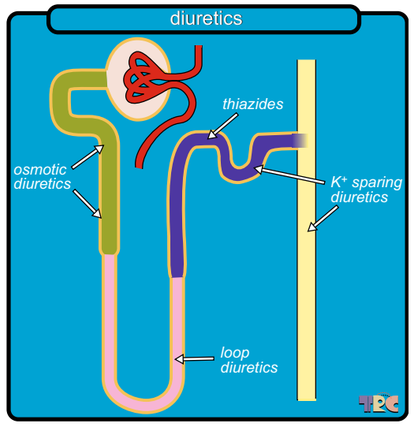
TRC is one of the most accessed teaching resources in the Netherlands with more than 2 million page accesses on the internet and more than 17.000 downloads of the apps worldwide. The students clearly adopted the system much faster than the teaching staff, who often went on with using their own materials. Generally, adoption of the system coincided with the development of internet technology and adapting the original system to this was key. The open system philosophy is essential. The TRC app was written by a medical student to facilitate his own learning and is since 2012 available (for free) in the App store.

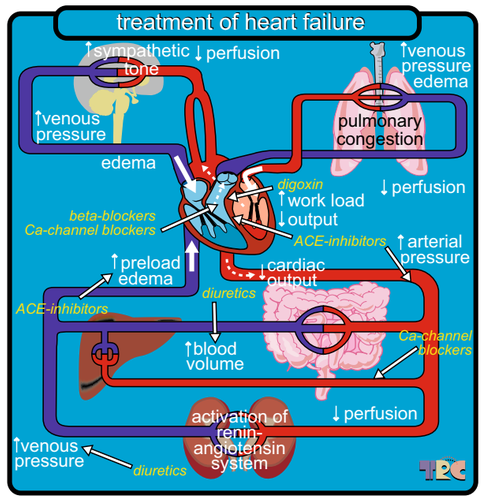
CLINICAL PHARMACOLOGY AS SPECIALISATION

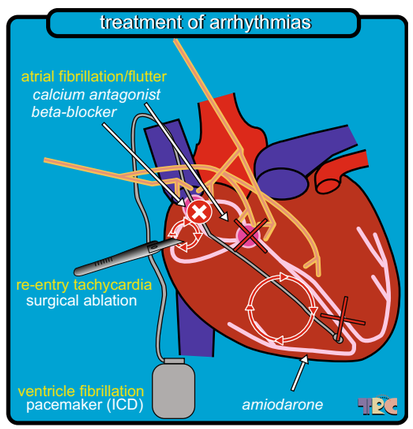
At CHDR all research fellows also participate in the training to become a board-certified clinical pharmacologist. The postgraduate course in clinical pharmacology is a special training for physicians and graduates with biomedical/ pharmaceutical background who want to specialize in pharmacotherapy and clinical research. It can be done in one year full-time, or spread out over several years. The curriculum includes various 'hands-on' courses and practical training in conducting clinical studies in healthy volunteers and patients and learning about the science behind it. Moreover, clinical work, advising doctors about the choice, dosage, adverse effects and interactions of drugs are part of the program. As clinical pharmacologist, you can join the grand rounds in the internal medicine department and discuss the pharmacotherapeutical choices afterwards.

INTERNSHIPS IN CLINICAL RESEARCH PRACTICE

CHDR has created an education model in which the research institute serves as an interface for university and industry biomedical training. The training program primarily aims to convey knowledge, skills and experience in human drug development while giving the students opportunity to experience the scientific method first hand. In a typical year, 50 applicants will compete for up to 15 student research positions. Student researchers may apply from any country







or training background as long as they can demonstrate being a self-directed learner, having a strong command of the English language and possessing a reasonable familiarity with the research process. Preference is given to students able to train for periods of at least 12 weeks. Once accepted, students are paired with a supervisor who is responsible for assessing the student's performance and level of completion of both the student's individual scientific and CHDR's training plans. The research student is also provided with a trainer who assists students in day-to-day guidance for completion of the research training. Students are expected to attend and participate in the clinical pharmacology lecture series and monthly research discussions to facilitate their exposure and understanding of various research methodologies and the drug development process. Scientific papers are discussed in journal clubs in order to stimulate critical thinking. Lastly, due to the number of activities ongoing at any one time, students are expected to pitch in whenever needed, for example they also facilitate and help to conduct practical courses or seminars in basic teaching courses, further diversifying their experience. The research internships are concluded with an oral presentation and a written report, that ideally leads to presentation at international conferences and publication in peer-reviewed journals.

Scan this code with your iPhone or iPad and get free access to the fully functional TRC pharmacology content.

1 Franson KL, Dubois EA, van Gerven JM, Cohen AF. Development of visual pharmacology education across an integrated me-dical school curriculum. J Vis.Commun.Med 2007; 30: 156-161.

2 Franson, K. L., Dubois, E. A., Meenhorst, P. L., and Cohen, A. F. The 6-step: validation of the Dutch national standard for a therapeutic plan. Basic Clin.Pharmacol.Toxicol. 101 (suppl.1), 33. 2007.

3 Rissmann R, Dubois EA, Franson KL, Cohen AF. Concept-based learning of personalized prescribing. Br J Clin Pharmacol 2012; Epub ahead of print.

4 Franson KL, Dubois EA, de Kam ML, Cohen AF. Measuring learning from the TRC pharmacology E-Learning program. Br.J Clin Pharmacol 2008; 66: 135-141.

Data management at CHDR – more than promises

Data are the lifeblood of a research organisation. Good data management helps to increase data reliability and maintain data integrity and is essential to meet international standards and regulations. To be able to do that in the pioneering early 1990s, CHDR developed its own software. It first became one of the flagships of the organisation, then it needed an internationally oriented company of its own: Promasys.

In the mid-1980's, just before joining CHDR, Adam Cohen was involved with the data management of large clinical trials at Wellcome. These data were 'managed' in the company mainframe and it took about a year's worth of programming effort for the data to be entered - let alone reviewed or analysed. To be able to draw any conclusions, in 1986 the possibility was discovered to do a shadow form of data management (obviously strongly forbidden) using copied software from the AMC cardiologist Ru Koster who was a principal investigator in these studies. Wellcome was not exactly amused, but had to rely grudgingly on these unofficial data for important decisions, as the data in their own mainframe were inaccessible – even though they were perfectly safe.

When Adam joined CHDR to become its CEO, he saw the need for a computer system in which the data collected during the conduct of clinical trials could be entered and managed efficiently, and, importantly, from which the data could also be extracted easily, while maintaining overall data reliability. Systems used in the pharmaceutical industry at the time were centralized and inflexible. In 1988, no fully developed and practically usable data management systems were available on the market yet. Therefore the decision was made to develop a system in-house. It was specified that it needed a user friendly, efficient interface that reflects the actual trial workflow, the data management process, and optimal and controlled data storage functionality. And it had to operate on a Local Area Network with the capacity of those days (which was ludicrously small compared to the data handling capacity of toy store computers these days).

TOWARDS PROMASYS 1.0

It is a place for the flow of the global level and in an on theJos Hennen was hired. He was a biologist and IT systems specialist, and he soon came to be one of the central driving forces behind the clinical data management system. He still is responsible for its software development today. Together with Adam and the other staff of CHDR he laid down the basic requirements for the system - the term 'user requirements' it was not as common in those days - and started developing a prototype.

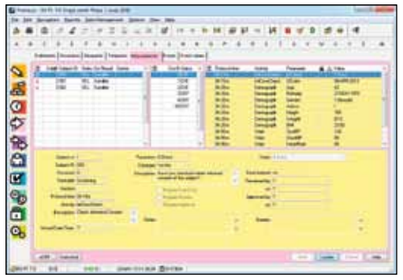
Jos first started working in Oracle. He attended three Oracle courses, but he soon found out that Oracle, in spite of its promises, was not (yet) capable of being operated in a local area network. As already told, this was a core requirement to ensure flexibility on the work floor while maintaining central control and protection of the data. After review of the available database solutions, Progress, a relational database management system with a LAN version, was selected as the platform in which CHDR's data management system would be developed.

STUDY LIFE CYCLE

In 1990 the first version saw the light as 'Promasys', derived from Protocol Management System, a name that was also intended to express hope for the future. It ran under MS DOS, on a server with only 512 KB of memory, in a LAN environment. It contained many of the functions that are still available in Promasys today: a table with protocols or individual clinical trials, a table with subjects, the concept of occasions or study visits, the concept of a timeline and a structure to capture variables with predefined attributes. From the beginning Promasys featured a robust audit trail. User access to the system and the data was managed through a mechanism that dynamically adjusts the user's access rights based on his functional role in the organization and on the stage in which the clinical trial is at a particular moment. This mechanism, called the Study Life Cycle, is still at the core of Promasys' data quality and integrity support functionality, and is unique in the world of clinical data management systems.

A

B



C

D

E

F

A The Promasys team during a training session for the World Health Organisation in Thailand. Promasys was used to manage a very large measles vaccine trial in India.

B The old DOS interface
C The Windows Client on a regular PC
D Fully integrated web interface allowing data management anywhere

E And finally the ultimate in paperless trial management. The iPad APP!
F Scan this code with your iPad and try the system out yourself!

Other functionality to support the workflow of a clinical research organization was already available in the first version, such as the option to print work lists for the trial nurses and labels for the blood sample tubes, or the function to register work hours, salary information and costs of trial activities. From the start, it had been a key requirement that users should be able to do everything, including setting up new studies, creating data collection forms, and extracting data, without having to do any programming. This has since been a central thread in the development of Promasys.

PROMASYS AS A COMMERCIAL PRODUCT

With the growth of CHDR and the diversification of the work, and with the increase in regulations and legislation governing clinical trials, the requirements for Promasys increased and throughout the 1990s additional functionality was developed. This was also the time when the world started moving away from DOS based systems in the direction of GUI (graphic user interface) applications, and it was inevitable that a Windows version of Promasys had to be developed, which in essence meant re-writing the application completely.

Promasys version 4.0 was the first Windows version which was released in 2004. While the result was very satisfying and generated much enthusiasm among the users at CHDR, it also had become clear that the development of a mature software application required focus and development capacity. Moreover, the fact that the development of Promasys was still dependent on one person carried a risk for CHDR's operational continuity. The way to eliminate this risk was sought in broadening the basis of Promasys by finding customers outside CHDR that would be willing to pay for the application and thus share the benefits and the risks.

An external consultant was contracted to conduct a market analysis and evaluate the marketability and sustainability of Promasys. The survey included academic research organizations and commercial contract research organizations both in the Netherlands and abroad. The conclusion was that there was a considerable market for Promasys, whereby 'the most attractive market segments for releasing Promasys are the academic and Phase I/IIA CRO market segments. The marketing strategy for Promasys will optimally play out this feature against competing vendors. The academic segment will therefore be targeted first, as this segment has the lowest level of data management support, and no commercial vendor is active in this segment. After breaking into the academic segment the Phase I/IIA CRO market will be targeted leveraging Promasys' track record in academic hospitals. Here Promasys can build on its feature of being the only package supporting both the workflow and the data management process.'

In 2004 a company was established: Promasys BV (Co., Ltd.). The first year was devoted to setting up the company, developing promotional material and developing a marketing and sales strategy. At the same time software development activities were continued. Business development was done more or less as a side job by the business developer of CHDR. It soon became obvious that success would depend on a more focused and dedicated BD approach. In January 2006 Wolf Ondracek joined Promasys as general manager with a primary focus on business development and sales. For many years Wolf had worked as a consultant to CHDR, among others working together with Adam on developing an infrastructure for comparative clinical pharmacology trials and bridging studies between Japan and the Netherlands. To date, Wolf is still heading the Promasys organization.

By the time Wolf joined Promasys, CHDR had two external customers: a Dutch CRO with offices in the Netherlands and in Spain, and a department in the LUMC. The initial business plan of 2005 had been based on the strategy that the first external customers would be located in the Netherlands. From there, Promasys would gradually expand into other European countries, and subsequently into Japan and the US. Reality proved different.

EXPANDING TO ASIA

Thanks to CHDR's academic network, and with the help of good timing, Promasys was introduced in Korea in 2006, where the government had just decided to invest heavily in building a clinical trials infrastructure, as part of its strategy to reduce the dependency on the production industry and promote the transition to a more knowledge based economy. A number of university hospitals was appointed to become regional clinical trials centers, and they also received funds to realize this. Attracted by the cost efficiency and the built-in functionality for quality control and compliance with GCP and regulations, 6 university hospitals decided to purchase Promasys almost in one go. Among them was Seoul National University Hospital, which is still one of the most active users of Promasys to date.

Adapting to the Asian market also required changes in the program itself. Promasys had not been designed with Far Eastern customers in mind, so in 2006 the system was not

capable of handling non-western, or so called double byte character based languages. This functionality, called Unicode support. was quickly developed and in the second half of 2006, Promasys was ready to accept data values in any language, so that the new Korean customers could also enter values and text in Korean. This is noteworthy, because it marked a new era in the development of Promasys software.

Until 2006, the software development had been exclusively dictated by the needs and requirements of CHDR. But from now on, external customers increasingly were going to influence the development roadmap. The guiding principle has been and still is to avoid developing tailor made solutions for one customer. Instead, requests for the development of new features and functionality are evaluated on their relevance for all Promasys customers. In other words, development decisions were based on market considerations and the market was no longer restricted to CHDR alone.

In 2007 Promasys welcomed its first customers in Japan, when 3 academic hospitals belonging to the JClipNet (short for Japan Clinical Pharmacology Network) consortium choose Promasys as their data management platform. One of these is Showa University Hospital where Eiji Uchida, once a post-doc research fellow at CHDR, is professor in pharmacology. Prof. Uchida has been a great supporter and promoter of Promasys ever since. In the same year, a collaboration was set up with Colombo based Kingslake Engineerings Systems, whereby Kingslake became Promasys distributor in the Indian region, consisting of India, Malaysia and Sri Lanka.

Also in that same year, and as a result of the collaboration with Kingslake, the World Health Organization selected Promasys as the data management platform for its Special Programme for Research & Training in Tropical Diseases. Through this program, WHO supported the building up of an infrastructure for high quality and compliant data management in developing countries. In a special intensive training program run in February 2008 at Thammasat University in Bangkok, 22 clinical trial professionals from 7 countries in Asia and Africa where trained to become advanced users of Promasys software.

EXPANDING TO LATER PHASES OF CLINICAL RESEARCH

Many of the new customers of Promasys used the software for later phase, often multi-center clinical trials. This led to the development of functionality to support multi-center studies, another example of software development that was driven by the needs of organizations other than CHDR.

With university hospitals in Italy (Pisa) and Germany (Heidelberg), Promasys gained some ground in Europe outside of the Netherlands. An important milestone was reached in 2009 when Peking Union Medical College Hospital, one of the top academic hospitals and most prestigious clinical research centers in China, selected Promasys for its clinical pharmacology research center.

In 2010, Promasys got its first pharma customer, with Mumbai based OncoRx, and oncology focused Indian pharmaceutical company. That same year gave birth to the WebCRF, a standard browser based module for electronic data collection. A large part of the software programming for the WebCRF had been outsourced to Promasys' partner Kingslake. The WebCRF, Promasys' first EDC solution, does not require any software installation and therefore is particular suited for data collection in multicenter studies. Because now it was possible to capture data electronically without first collecting data on paper forms, it had become necessary to have functionality for signing off data items electronically, in order to maintain compliance with CFR 21 Part 11. This functionality was released together with the first version of the Webcrf.

EDIT CHECKS

The larger part of software development activities in 2011 was devoted to the development of edit checks functionality. This functionality is designed to provide immediate feedback to the user entering data into the system based on user-defined conditions, and across multiple data items. In line with Promasys' no-programming principle, the goal and challenge was to come up with a solution that allows users to set up complex rules and relations between data items without having to do any programming. Version 6.2 which was released early in 2012 met this goal beautifully with a point&click editor for creating even the most complex edit checks.

In the second half of 2011, St. Antonius Hospital, a non-academic research oriented hospital in the central parts of the Netherlands decided to buy Promasys as a solution for the data management of its investigator initiated trials. In the same period, the SANTEON group of so-called top clinical hospitals, of which St. Antonius is also part, started a pilot with Promasys for a large multicenter study. In this case Promasys is provided as turnkey service, which includes hosting of server hardware and software, setup of the clinical study database, user account management and training. This was the first time that Promasys is provided on a SaaS (Software as a Service) base.

EXPANDING, INEVITABLY, TO APPLE

Already before the release of version 6.2 early in 2012, plans were on their way to develop a mobile application for data collection. Because of its reliability, high level of security and robustness, the iOS based iPad was selected as the device for which the mobile application would be developed. The development of the app was outsourced to a specialized company in Eindhoven, but the requirements and the design of the app were defined and controlled from our Leiden office.

Increasingly it became obvious that managing complex software development projects, which now involved two different contract development partners, and at the same time supporting existing customers and trying to find new customers in faraway countries became ever more challenging. Therefore, throughout 2011 and 2012 much energy was put into further building up a sales and support channel in the countries that had become our most important regions. The collaboration with Kingslake in the Indian region was intensified, a sales agent was set up in China, and the customer support and sales team in Japan that consists of only two persons, was strengthened through an alliance with the IT oriented local CRO AcroNET Corporation.

At present, these efforts are beginning to bear fruit. In the last half year, two new customers were added in India, one of which is the Clinical Development Services Agency, which is part of an organization that resides directly under the Government of India. In Japan, Promasys was implemented recently in Osaka University Hospital and Hokkaido University Hospital and is about to be implemented in the Kyushu Cancer Center in Southern Japan. And in China two academic hospitals have been added to the Promasys user's community in the first few months of 2013.

A major new version has been released in the second week of May of this year, which includes the first version of the Promasys iPad app. Two customers, both in Japan, have already implemented the iPad app in a test environment, and have started with their internal validation process.

In the past 25 years, Promasys developed from an MS DOS based CHDR in-house system to a clinical data management solution that is used in more than 30 organizations in various parts of the world; a solution that helps these organizations to increase data reliability and maintain data integrity in an affordable way, and helps them to be compliant with international standards and regulations; that allows them to be responsible for and maintain access to their clinical trial data; and that now offers its users an innovative solution for data entry and subject management on a mobile device.

Question-based approach to drug development

IN THE PAST DECADES, DRUG DEVELOPMENT HAS BEEN CONCEIVED OF AS A SUCCESSIVE SERIES OF STEPS OR PHASES. THIS APPROACH HAS WORKED WELL IN THE PAST, BUT NOW, ITS SUCCESS RATE IS RAPIDLY FALLING. PROCESS IN WHICH SEVERAL QUESTIONS HAVE TO BE ANSWERED, NOT NECESSARILY IN A PRESET SEQUENCE. USING THIS NEW PARADIGM MAY SAVE COMPANIES MILLIONS OF DOLLARS, AS IT CAN MAKE THE DIFFERENCE BETWEEN CURING PATIENTS OR LOSING LAWSUITS.

The drug development business is extremely risky, time-consuming, and cost-consuming. Over time, the intrinsic risks of successfully developing new pharmacological treatments have increased and the claimed costs and development times have exploded. These changes have had a profound effect on the way society perceives drug development and how drug companies are forced to market their drugs to fuel the development process of novel compounds and fund failed projects.

Many efforts have been made to optimise the process of drug development, with the vast majority of efforts targeting discovery, lead optimisation, lead selection, biomarker inclusion in early evaluation studies, early proof-of-concept studies, and so forth. Sequencing the human genome has also provided us with an enormous number of possible targets for novel treatments. Although this has significantly boosted the number of investigational compounds, it has not reduced the intrinsic risk of drug development.

Traditionally, drug development has been organised linearly, from discovery to lead selection and optimisation to preclinical development. Clinical development is traditionally explained in phases I to IV, roughly addressing safety & tolerability in phase I, proof of concept in phase II, confirmatory phase III studies, and post-marketing approval phase IV studies. The traditional large pharmaceutical companies driving drug development are often organised similarly. Net Present Value is a classic project value estimation tool that allows pipeline project comparison, development monitoring, and overall financial management. Net Present Value's core drivers are costs, revenues, and time, which are not uncommonly (but erroneously) seen as primary drivers of the drug development process. Any project that historically only has an a priori chance of success of around 12-13% should be primarily managed by this risk (12-13% is an industry-used historical success rate of a given compound navigating from phase I to successful market introduction). Full incorporation of risk into value estimations is obligatory, and every effort should be made to identify and tackle the (scientific) origin of this attrition rate.

As a first step when incorporating the risks of clinical drug development into evaluations of drug development programmes, Real Options Value Estimation (as used in other high-risk, high-cost industries, such as the oil drilling industry) can be used to describe the entire process using, for instance, historical risk data. Although this reduces project values to more realistic proportions, it provides no insight into the scientific origin of the uncertainties surrounding the development of novel treatments. Hence, attempts were made to apply Real Option Value Estimation to relevant scientific issues instead of clinical phases.

Developmental phases are more rationally described by their respective scientific content. In other words, the questions addressed by studies reflect the development process more accurately. The successful development of a new drug requires that a number of generic questions be answered:

- **Do the biologically active compound or active metabolites reach the site of action?**
  Related issues: Absorption, route of administration, bioavailability, distribution, tissue distribution, accumulation, action site penetration, metabolism, active metabolites, metabolic routes, hepatic or renal excretion, clearance, half-life
- **Does the compound cause its intended pharmacological/functional effect(s)?**
  Related issues: Effects related to mechanism of action; additional effects of primary pharmacological activity; effects of secondary pharmacological activity; other, undesirable effects
- **Does the compound have beneficial effects on the disease or its clinical pathophysiology?**
  Related issues: Effects on relevant physiological systems, effects on disease, undesirable clinical effects
- **What is the therapeutic window of the new drug?**
  Related issues: Clinical effects at tolerated dose, dose regimens/intervals, controlled drug delivery, forgiveness
- **How do the sources of variability in drug response in the target population affect the development of the product?**
  Related issues: Compliance; pharmacogenomics; ethnic differences; concomitant medication; variability in pharmacokinetics, pharmacodynamics, and disease state

Although the questions themselves are generic and may elide multiple sub-questions, the development risks and the effort required to answer the questions is unique for each potential new pharmacological intervention. By introducing clinical development questions to describe the development process, an interesting new factor is introduced: the sequence in which these questions are addressed. Five questions no longer have to be addressed linearly in phases, but can be addressed in any order. More specifically, there are 5! = 120 ways to order these five questions.

To optimally order questions for every individual investigational product, the distribution of the risks and required effort to address those risks (e.g., costs) is to be discussed by development teams and everyone involved in designing development plans and individual studies. The everlasting discussions about the true/absolute risks and true/absolute costs of drug development are secondary to discussions in which the risks are relevant to the individual product. This approach conceptually changes the way we look at drug development or, more accurately, the approach provides us with a tool to value innovation and knowledge generation. Decision tools can help in calculating the optimal order for each set of costs/efforts. Finally, the questions need to be transferred to individual studies that use the best designs and methodology to answer them.

In the 2003 CHDR thesis, 'A Question-Based Approach to Drug Development', this is exemplified in several ways. It also calculates the added value of biomarker research: knowledge increases appropriate biomarker selection, which in turn increases the chance that a drug will exhibit effects. While in the old paradigm, additional studies are merely considered as a source of additional costs and time delay, timing additional questions can reflect additional value in the question-based development (QBD) paradigm. Another example in which QBD offers insight into rational decision-making is when determining whether it is feasible to perform bridging studies with Japanese populations. Finally, the thesis describes how determining critical questions early increases QBD project values. These examples illustrate that the combination of success probabilities and accompanying costs to answer the questions are a unique data set that can vary with different compounds. Even if the overall probability of success and the overall costs are the same, these unique sets dictate an optimal development strategy. The sequence of relevant questions should serve as a priority list in the development of new drugs throughout the program. Regular updates of all probabilities and costs will optimally direct the development process.

Since 2003, several pharmaceutical companies, regulatory agencies, and universities have adopted the question-based approach, although fully embracing the entire concept will probably take some additional time. Question-based drug development has always been the basis for studies performed at CHDR and consultancy by CHDR staff. The thesis provides us with a tool that bridges financial project management and drug development science to explicate what we subconsciously already knew: there is great value in addressing relevant research questions at the right time. Moreover, the thesis aids in rationalising what 'relevant research questions' and 'right times' are. Developing novel drugs is not best described by any linear process, but rather by a knowledge-generating process that is tailored to each individual project and therefore has its own individual hurdles to overcome.

PERSPECTIVES

OPINION

Developing drug prototypes: pharmacology replaces safety and tolerability?

Adam F. Cohen

Abstract | New medicines are designed to bind to receptors or enzymes and are tested in animal cells, tissues and whole organisms in a highly scientific process. Subsequently they are often administered to human subjects with tolerability as the primary objective. The process of development is considered to be linear and consecutive and passes through the famous four phases of development (Phase I–Phase IV). This is efficient for those projects for which the uncertainty about the development is low. There is, however, an increasing number of new prototypical compounds resulting from the increased biological knowledge with a high level of uncertainty. For these prototypical drugs development has to proceed in a much more adaptive manner, using tailor-made objectives, the development of special methodology and a cyclical rather than a linear type of project management.

In 1785 a physician from the county of Shropshire in England, UK, discovered that extracts from the leaves of the foxglove (*Digitalis purpurea*) had an impressive effect on oedema. He did not know that the oedema was caused by heart failure and described foxglove leaves as a diuretic from his observations of the mobilization of the extracellular fluid as increased urine output. William Withering wrote a masterpiece, describing the clinical effects and side effects of digitalis leaves in great detail. His careful clinical observations followed by clinical experiments with dose and administration forms were done in a systematic manner and interpreted with great skill. *The Account of the Foxglove and its Medical Uses* is a tribute to the power of logical scientific reasoning in an age of limited technology[1] (FIG. 1).

Withering not only performed brilliant clinical science, using the limited tools available to him, but he was also years ahead of his time by indicating the need to study drugs by other modes of analysis than just the observation of clinical signs. Lacking these, "their virtues therefore must be learnt, either from observing their effects upon insects and quadrupeds; from analogy, deduced from the already known powers of some of their congenera, or from the empirical usages and experience of the populace." Note that this country doctor predicted biomarkers, 'me too' medicines (that is, drugs that largely duplicate the action of existing drugs) and clinical trials, as well as animal toxicology being applied to new medicines.

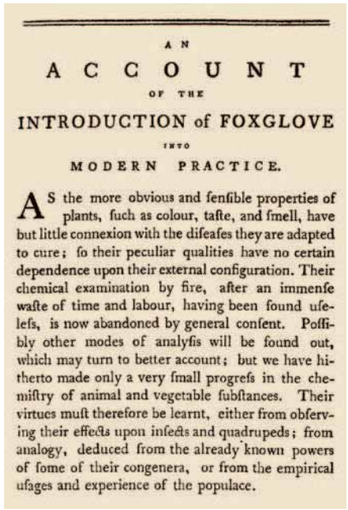
Today many of the technologies that Withering hoped for are in the toolkit of the clinical drug developer. Unfortunately many of these are not always used in the early development of new medicines and Withering, if faced with a standard clinical trial today, would see a surprising similarity to his own drug research. This Perspective will cover the historical reasons for this and provide some new concepts for drug development on a pharmacological (knowledge about the biological effects of the drug) base rather than the pure process (time) base that is currently still predominant. Not all new drugs require such a novel approach and it will also be attempted to indicate a system to differentiate between new drugs with low uncertainty and new drugs with high uncertainty, projects which I term prototypical.

Drug development as a linear process

Standard textbooks of drug development describe the development of a new drug in different phases[2,3]. This neatly consecutive discovery process starts with a therapeutic concept, which is generally based on existing knowledge of the aetiology of a disease. This leads to the well-known steps of target selection, target validation, lead identification and lead optimization, which may result in a drug candidate. This candidate undergoes preclinical development and when sufficient data are acquired to determine suitability for administration to humans, a new sequence of chronological events ensues, which can be divided into four clinical phases. This whole sequence can be described in a linear manner — with compounds progressing forwards through each step until the compound either reaches the market or its development is terminated.

However, in practice this process is not appropriate in all cases, as there are instances in which it does not lead to the drug being appropriate for the indication or the correct predication of dose. A large proportion of registered drugs require dosage adjustments[4] or display pharmacological[5] or toxicological effects that subsequently lead to discontinuation of the product. For example, only the lipid-lowering effects of the cholesteryl ester transfer protein inhibitor torcetrapib were pharmacologically studied in detail[6]. Effects on aldosterone and blood pressure, which may have led to its demise in the clinic when the compound did not produce the expected effect on mortality, were only studied much later[7].

The question is therefore whether the traditional four clinical phases of drug development are still the right approach for all projects. Indeed, the US Food and Drug Administration (FDA) abolished this concept as a basis for classifying clinical trials — most emphatically in a guideline in 1997 (REF. 8) — replacing the classification by much more appropriate study types



AN
ACCOUNT
OF THE
INTRODUCTION of FOXGLOVE
INTO
MODERN PRACTICE.

AS the more obvious and ſenſible properties of plants, ſuch as colour, taſte, and ſmell, have but little connexion with the diſeaſes they are adapted to cure; ſo their peculiar qualities have no certain dependence upon their external configuration. Their chemical examination by fire, after an immenſe waſte of time and labour, having been found uſeleſs, is now abandoned by general conſent. Poſſibly other modes of analyſis will be found out, which may turn to better account; but we have hitherto made only a very ſmall progreſs in the chemiſtry of animal and vegetable ſubſtances. Their virtues muſt therefore be learnt, either from obſerving their effects upon inſects and quadrupeds; from analogy, deduced from the already known powers of ſome of their congenera, or from the empirical uſages and experience of the populace.

Figure 1 | **The account of the foxglove and its medical uses.** William Withering laments the lack of chemical methods available to study drugs and accepts that the second-best method is the study in whole animals and in humans. Figure is reproduced, with permission, from REF. 45 © (1985) Oxford University Press.

(TABLE 1). It is of interest why this concept of the four phases of drug development is being perpetuated virtually unchallenged, even by the authority that issued the new guidelines. Why does the traditional model still exist and are there possible alternatives?

The heyday of the linear model

It is debatable whether the linear clinical research process, which may have been historically appropriate, is suitable for all the current compounds in development. At the beginning of the 1990s an analysis by the stock analysts Lehman Brothers sent ripples of concern through the pharmaceutical industry. To fund the level of investment in research and development of the pharmaceutical industry of that year, sales of future products had to increase to an unsustainable level, unless each company produced approximately two products a year with a turnover of at least a billion dollars each.

This was the era of the angiotensin-converting enzyme inhibitors and the cholesterol-lowering agents that were reasonably safe, could be used widely for many indications and were marketed at a relatively high price. So the feasibility of marketing several large turnover products frequently and, above all, rapidly seemed realistic. Speed and progression of the clinical trials were therefore essential in the development of these products.

This required strong attention to efficiency and a linear development model with consecutive phases, as is appropriate in such cases, when the unforeseen uncertainty about the project is low[9]. At the start of a project there is always uncertainty but in some cases this uncertainty can be fairly easily and conclusively resolved. In the course of this article uncertainty in a project is defined as a high level of foreseeable uncertainty (that can be resolved) and also a high level of residual uncertainty (that cannot be resolved). The residual uncertainty category is in other disciplines often termed the unknown unknowns (or unk unks). I refer the reader to the excellent book by Christoph Loch about risk management in projects for further theoretical background[10].

In a linear model many functions, such as the trial design, the execution of an experiment, the reporting and the publication, can be standardized and separated into distinct specialized organizational units, which increases the efficiency of the drug development process. The separation of scientific departments from operational departments in pharmaceutical companies — that were still integrated in the 1980s — was a logical consequence of this. Furthermore, the outsourcing of the operational performance of a clinical trial in its entirety was made possible by the growth of the process-oriented contract research organizations[11].

The demise of the large turnover product rofecoxib (Vioxx; Merck)[12], after having been marketed, confirmed mounting fears that this model (sometimes now called the blockbuster model) was unsustainable[13]. This led to a realization that there was much more uncertainty in the development of new drugs than perhaps previously considered, even for compounds such as rofecoxib, which could be considered an incremental innovation of the traditional non-steroidal anti-inflammatory drugs.

The observed drop in the number of innovative products reaching the patient led to much reflection and publications about the potential causes. Problems were ascribed to a wide range of culprits, which included the hypothesis that all the easy targets were being covered ('low hanging fruit') and issues related to managerial and organizational concerns[14]. There is no doubt that the number of medicines being marketed each year is not increasing, despite an increase in the research and development budgets of the pharmaceutical industry[15]. Conversely, there is also much evidence that the rapidly increasing knowledge about disease mechanisms will produce a large number of highly innovative drugs to be evaluated, but that the evaluation process will take longer than expected or hoped[15,16].

Adaptation of the model

The development of innovative compounds is rife with unknown unknowns. This requires a more innovative approach to development[10,17] than consecutive, phased project management, which is intended to deal with low uncertainty projects. Not all drugs to be developed are at the same level of innovation. A compound that is chemically innovative may not affect a new biological mechanism or be a therapeutic innovation. These compounds have less uncertainties in development and require a different project management style compared with an entirely (that is, chemically, mechanistically and therapeutically) novel molecule. Such novel compounds are termed prototypical in this paper; in contrast to less innovative standard compounds (BOX 1). In fact such a differentiated approach to prototypical versus standard product development is quite common in the electronics and software industry and has a solid underlying theoretical basis[9,18–20].

Development of standard products that are directly intended for the market (as project uncertainty is deemed to be low) is appropriate for projects that can have the remaining uncertainties removed in confirmatory research. Any loss of time in getting the product to market is loss of sales and the priority of the project is high speed and low cost.

Industrialization of the processes needed to perform the research, through the differentiation of functions in different organizations, is possible in these cases and the transfer of technology between these organizations is easy. For example, in such cases the writing of a standard study protocol can be done by medical writers, the regulatory submission and discussions by a consultant, the performance of the study in many different countries by a contract research organization and the reporting by a statistical consultancy group.

By contrast, a prototypical project is not directly intended for the market. This is because uncertainties (unknown unknowns) need to be identified and subsequently removed by redesigning of the molecule or by returning to an earlier stage of the development plan or even by the performance of new animal or laboratory tests (that is, back to the drawing board). The priority

Table 1 | **Classification of study objectives according to FDA clinical trial guidelines**

Objective of study	Study examples
Human pharmacology study	
• Assess tolerance • Define and/or describe pharmacokinetics and pharmacodynamics • Explore drug metabolism and drug interactions • Estimate drug activity	• Dose tolerance studies • Single and multiple dose pharmacokinetic and/or pharmacodynamic studies • Drug interaction studies
Therapeutic exploratory study	
• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study designs, end points and methodologies	• Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological end points or clinical measures • Dose–response exploration studies
Therapeutic confirmatory study	
• Demonstrate and/or confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit–risk relationship to support licensing • Establish dose–response relationship	• Adequate and well-controlled studies to establish efficacy • Randomized parallel dose–response studies • Clinical safety studies • Studies of mortality and morbidity outcomes • Large simple trials • Comparative studies
Therapeutic use study	
• Refine understanding of benefit–risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendations	• Comparative effectiveness studies • Studies of mortality and morbidity outcomes • Studies of additional end points • Large simple trials • Pharmacoeconomic studies

FDA, US Food and Drug Administration. This table is adapted from REF. 8.

in these projects is on the knowledge and the integration of information from many sources involving learning research rather than confirmation. It is best done by groups of specialists in one location, as technology transfer of part of the process to a specialized organization is generally impossible as a result of the many remaining uncertainties.

The concept of concurrent engineering (in which stages are not consecutive but parallel) and prototype learning cycles has been rarely applied in drug research, although it is used regularly in engineering and software development. In line with this, it was suggested some 13 years ago that drug development should proceed in so-called 'learn and confirm' cycles and that a change in the style of project management is necessary[21]. Unfortunately this view was not widely accepted or practiced. This is perhaps not surprising because most of the previous generation of marketed products with big turnover did not require this approach. It may therefore be useful to make a differentiation between standard and prototypical projects and to tailor the development process and knowledge management to the project, rather than adapting the project to a rigid process.

Experiments with prototypes

The proposed method of differentiation between standard and prototypical drug development is shown in FIG. 2 as a matrix with two dimensions. The first dimension of the matrix describes the strength of the knowledge about the linkage between the biological mechanism of a drug and the clinical effect (defined as an effect on 'feelings, function or survival'). For example, the link between the inhibition of the enzyme involved in inflammation, mitogen-activated protein kinase, (that is, the biological mechanism) and an effect on joint destruction in rheumatoid arthritis (that is, the clinical effect) is not established for an inhibitor with a novel mechanism of action. A standard drug has by definition a 100% linkage between its biological mechanism and the clinical effect, as it has already been established for the original compound.

The second dimension of the matrix is the availability of methods that allow this link to be established, which I call a linkage marker. This could be a biomarker or another measure, such as the plasma concentration of the drug. A generic drug has a near perfect measure in the plasma concentration and bioequivalence to an existing marketed compound. On the other side of the spectrum is the entirely prototypical compound, which affects a new mechanism that cannot be evaluated with existing methodology. The inhibition of mitogen-activated protein kinase and its effects on cytokine release in relation to the concentration of a drug may require specialized development of the assay. Depending on the project, the marker (or group of markers) could be various measures, such as a questionnaire, a sophisticated brain imaging technique or the measurement of a cytokine in an unusual body fluid[22].

The task of a drug developer can then be simply described by moving the prototypical project from the lower left hand of the graph (FIG. 2) to the upper right hand through an understanding of the link between molecular mechanism and disease using innovative trials with a toolkit of markers. This approach suggests that the linkage marker toolkit cannot be developed and validated at the same time as the link between the biology and clinical effect is tested. Generally, the markers have to be developed ahead of the evaluation of the link. This in itself requires a different approach to project planning. Some of the activities to develop these markers have little to do with the development of the compound as a medicine, but much more to do with the methodology. If the fact that markers need to be developed ahead of the compound is not recognized in time serious delays in projects will occur as the technology is not ready when the project is. For non-prototypical projects this is less likely to happen.

No translational development in phases

Virtually all new compounds are of small molecular mass, chemically synthesized or large biologically-made molecules and most, if not all, are developed with the intention of having some molecular interaction with a receptor or an enzyme. These are normally evaluated preclinically in accordance with the scheme shown in FIG. 3. This logical progression of the acquisition of knowledge is disturbed when the compound is given to human subjects at the start of Phase I trials. At this point, according to standard teaching, the drug is first evaluated for its tolerability and safety. This is logical for a standard compound, as the only function of the first administration to humans is to confirm that the drug is indeed well tolerated.

For a prototypical compound a stepwise approach that confirms the intended pharmacological effect of the compound in human receptors, isolated cells and tissues is more appropriate, and is analogous to the studies done in the animal models.

Box 1 | **Standard versus prototypical drug development**

This box gives the usual properties of the 'standard' development programmes with regard to preclinical and clnical research. By contrast the rquirements for a solid prototypical drug are given.

Standard drug development

- Pharmacological experiments in animals done using dose–response relationships
- No concentration measurements in preclinical pharmacology
- No strategy for linking results from animal experiments to human pharmacology or physiology
- Link between animals and humans through the no observed adverse effects level (NOAEL) dose in toxicology studies in animal models
- No measurements of pharmacological or physiological drug effects in toxicological experiments
- First dose in humans determined by a fraction of NOAEL
- Only clinical observation of adverse effects in the first human experiments
- Dosing in humans until the tolerability level is exceeded
- Development is linear and as rapidly and as cheaply as possible

Prototypical drug development

- Concentration–effect relationship established in pharmacological experiments
- Clear predefined strategy that is based on the relationship between the scientific questions that lead to animal testing and the questions to be answered in experimental testing in humans
- Link between the effect of the drug in animals and in humans based on quantitative experimental results from animal and human receptors, cells, tissues and whole organisms
- Measurement of drug effects rather than side effects or tolerability in animal toxicology experiments
- First dose in humans based on pharmacological effects
- In addition to observation of side effects, quantitative measurements of drug effects from first dosing in humans onwards
- Extensive use is made of the fact that regulatory agencies allow the possibilities of exploratory trials, microdosing and other opportunities for obtaining information about the usefulness of a compound rather than its adverse effects
- Determination of tolerability of the drug is not a primary aim
- Development is cyclical, with maximization of information as a priority over speed and cost

In this way, the transition to humans should repeat some of the steps that were systematically taken during the preclinical phases of development. The FDA guidelines for exploratory investigative new drug studies may be of value for this[23]. The 'straight into human' approach might be considered too risky for prototypical compounds[24] as it involves no testing of the actions of the compound in human cells, tissues or organs before progressing to human subjects. By contrast, the animal experiments that are performed with the molecule follow a logical progression from molecular interactions to cellular effects, tissue physiology and finally effects on the whole organism. The quantitative aspects of this, using plasma concentrations and effect measurements, can be integrated using pharmacokinetic–pharmacodynamic models[22,25]. From this data, a dose that is likely to produce a pharmacological effect in humans can be estimated. This is still rarely done. For example, because there is generally no information regarding the plasma concentrations of drugs that produce pharmacological activity in animal models[25], it makes it impossible to predict the concentration–effect relationships in humans.

The 'straight into the organism' approach is also used when determining the potential preclinical toxicology in animal studies. The drug is generally given to two animal species in doses that are sufficiently high to induce toxic effects. A lower dose at which these effects do not occur is then established and this no observed adverse effect level (NOAEL) dose, diminished by a rather arbitrary safety factor, determines the human dose[26]. Moreover, the requirements to determine the pharmacological effects of the drug in the toxicological species are limited to the general requirement for the species to be responsive to the primary pharmacodynamic effect of the substance (see the document from the European Medicines Agency: *Note for Guidance on Repeated Toxicity* (CPMP/SWP/1042/99)).

For biological substances the relevant receptor or epitope has to be expressed in the species. It is nowhere stated in this guidance that this has to be experimentally confirmed in the repeated dose toxicity tests by ascertaining that this also leads to functional or physiological effects that are similar to those in humans. This theoretically allows the use of an animal species for toxicological tests in which the drug functionally lacks its primary biological actions, when for example, the receptor is expressed but has different functional effects in this species than in humans and hence will tell us little about its toxic effects induced by excess pharmacology. At this point it should be recalled that the research of Withering in 1785 was similar.

Tolerability and safety. Unattainable?

An ethical committee should reject protocols for studies in humans for which the methodology does not allow the objectives to be reached. I studied the Phase I studies submitted to the competent authority for clinical trials in the Netherlands in 2009 (the Central Committee on Research Involving Human Subjects). For this assessment the full protocols and investigative medicinal product dossiers of these studies were examined. The system in the Netherlands guarantees completeness of the data set as submission in the national database is required by law.

There were 26 Phase I studies in patients, of which 27% were first administrations of the drug to humans. Most of these studies (65%) were in cancer and virtually all protocols involved highly innovative therapeutic concepts and products. Yet, 85% of all these studies had as their primary objectives the safety and tolerability of the compound and 50% attempted to reach a maximally tolerated dose as its end point. There were 81 studies carried out in 4,754 healthy volunteers, of which 40% were first-in-human studies. All of these studies were performed using only safety and tolerability as the primary end points.

Only in 42% of the studies were biomarkers used at all, although generally they were used as a secondary end point and never as linkage markers. In 60% of the studies in which biomarkers were used at all, considerably more human pharmacology could have been done, either by more frequent assessment of these markers or by more pharmacologically appropriate ones to allow the measurements to be used in decisions about the potential activity of the compound. For example, in a protocol of a highly innovative analgesic compound with a new mechanism of action, no experimental pain model was involved. At high doses serious adverse effects developed in humans but it was unknown how these related to analgesic dosage, producing serious delays in the development of the

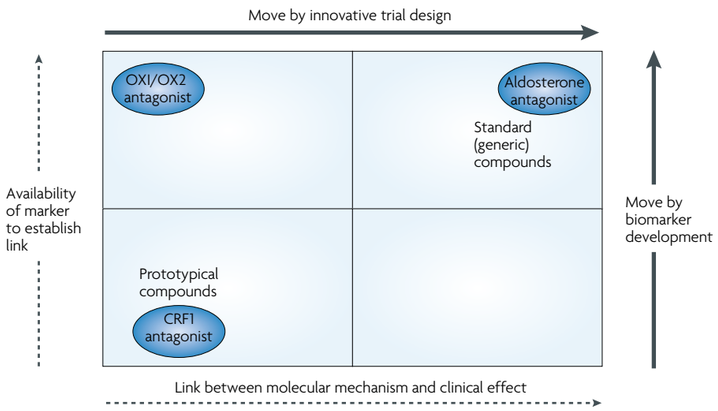


Figure 2 | **Determining the prototypical nature of a project.** An aldosterone antagonist, such as eplerenone, could undergo standard development because the link between the inhibition of the receptor and the clinical effects in heart failure are well known and the methodology to study this is mature. By contrast, a corticotropin-releasing factor 1 (CRF1) antagonist for social anxiety is prototypical because the link between this receptor antagonism and the beneficial effects on the clinical symptoms, as well as the methodology to study it, is not yet validated. The orexin 1 (OX1) or OX2 antagonist described in REF. 39 is an example of a prototype for which the methodology (sleep studies) is well established to show linkage between molecular action and clinical effects.

compound. It was remarkable that even for first-in-class biologicals — for which pharmacodynamic measures are generally an integral part of the first-in-human clinical trial protocol — there was limited evaluation of pharmacodynamic measures.

Virtually all of these first-in-human studies were done with highly innovative prototypical compounds. This situation is consistent with the apparent current state of affairs in early drug development. Even in cases when the human pharmacology of a new compound can be tested it is either not done or postponed to a later stage of development. In the data set that was studied, the objectives of the studies were generally standardized and did not seem to be dependent on whether or not the compound was innovative or to be dependent on the nature of its pharmacological intended activity. Further study of these phenomena in larger data sets is of interest to detect whether this is an international generalization.

Some compounds with excellent tolerability and stated safety profiles are neither safe nor well tolerated in the patient population as a whole and this is only identified late in development or after marketing of the drug. With most of these compounds a safety problem is identified that is relatively infrequent but serious. The probability of detecting this in a typical Phase I study with perhaps 10 to 20 subjects per dose level is too low and the studies are therefore seriously underpowered to detect safety issues[27] of importance when used in the whole patient population taking the drug. Small studies can detect frequently occurring tolerability issues and are useful for this, although such effects are generally pharmacological and are much more easily detected by quantitative measurements, rather than by event rates.

Tolerability can be determined in early drug-development studies but it is questionable whether this is useful (FIG. 4). The assumption is that the therapeutic dose of a medicine is more plausibly related to its pharmacological actions than to its toxic effects. The method of determining the therapeutic dose as a certain fraction of a toxic dose (the maximally tolerated dose) originates from a time when most drugs were relatively toxic (when these measures were probably closer together) and its value has been based on old literature[28,29] relating to classical cytotoxic drugs. Therefore this method only works for drugs with a narrow therapeutic margin for which the toxicity of the compound is linked to the clinically wanted effect. This is the case for the classical cytotoxic drugs because of bone marrow depression (the usual tolerability problem for these drugs) being a marker for an effect of the drug on rapidly dividing cells, but it is not applicable to any other modern medicines. Even the current generation of anticancer drugs is becoming increasingly selective.

The current methods of drug discovery tend to select compounds with a wide therapeutic margin and this renders the maximally tolerated dose method uninformative for such compounds. Although it is important to determine the clinical tolerability of a drug or its maximally tolerated dose, this measure may not be the first or the most important uncertainty that needs to be resolved for a prototypical drug. The relevance of the human toxicology rather than the human pharmacology of a compound is dependent on its perceived therapeutic margin. For example, there would be no disputing that attempting to determine the tolerability of healthy subjects to a penicillin derivative

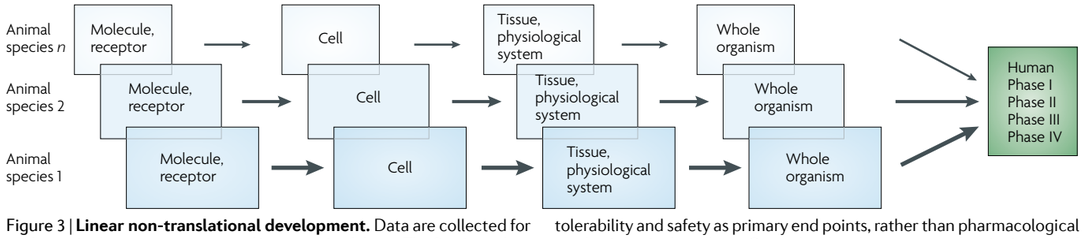


Figure 3 | **Linear non-translational development.** Data are collected for each species but are not connected in a meaningful way. The first introduction of the compound into humans is directly into the whole organism, using tolerability and safety as primary end points, rather than pharmacological or physiological markers. Once the development reaches its intended target species, humans, the experiments become increasingly empirical.

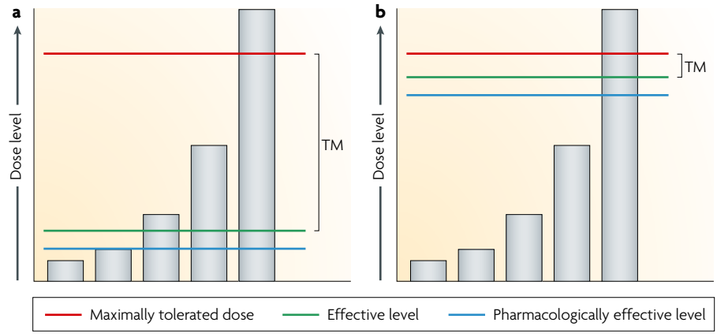


Figure 4 | **Representation of ascending dose study design.** A constant relationship between the pharmacologically active dose and the therapeutic dose is assumed in both situations. **a** | A maximally tolerated dose design is used for a drug with a large therapeutic margin. If a dose for further trials is chosen just under the maximally tolerated dose then overdosing will occur. **b** | The situation for a drug with a narrow therapeutic margin (that is, a classical cytostatic) is shown. The maximally tolerated dose is close to the effective dose level and in such a situation a reasonable estimate of dose is obtained. Note that the effective level is unknown at this early stage of development and if no pharmacological effects are measured only the maximally tolerated dose will determine the dose level in both cases. TM, therapeutic margin.

would be futile. In this case, knowledge of the inhibitory concentrations in a sensitive microorganism, in combination with the plasma or tissue concentrations of the drug, would determine the therapeutic dose.

Expensive lack of pharmacology

The potential danger of the standard approach to drug development can be illustrated using the 5-hydroxytryptamine (serotonin) receptor 4 agonist tegaserod (Zelnorm; Novartis), which was launched in 2001 for the treatment of irritable bowel syndrome and constipation. Early development was done in the standard manner, with attention to safety, tolerability and pharmacokinetics[30,31]. Although the drug was pronounced to be well tolerated and safe following the first studies in humans, it was withdrawn from the market in 2007 because of an increase in cardiovascular events (13 out of 11,614 people taking the drug versus 1 out of 7,013 people on placebo (source: FDA Centre for Drug Evaluation and Research). Although these adverse events might have been the result of some undetected vascular effect of the drug they could also have been the result of chance. The turnover from the drug decreased from US$561 million (growing at 34% per year) in 2006 to $88 million and then to zero. This produced an immediate loss of turnover, only in the first year after discontinuation, of $664 million (data from Astra Zeneca's annual report 2006).

Of the 388 publications about the substance only one dealt with its effect on coronary arteries[32] and no human pharmacological profile was established other than in the target organ, the gut. This was despite the fact that 5-hydroxytryptamine receptor 4 agonists are known to induce the release of vasoactive peptides, such as calcitonin gene-related peptide and substance P. The presence of detailed pharmacological profiling on the cardiovascular system in humans could have played an important part in the evaluation of the safety data and a potential defence against regulatory claims that the increase in cardiovascular events were related to the drug.

It is obviously impossible to say whether the availability of such pharmacological profiling would have made a difference in the final regulatory decisions and there are many other factors, such as the relatively low efficacy of tegaserod, which may have contributed to the final decision about withdrawal of the drug. The fact remains that human pharmacological data were not available and the study on the effect of tegaserod on human coronary arteries (which was negative) only appeared after its discontinuation. The mechanistic aspects of tegaserod in the gut were well studied but the study of collateral pharmacology, in animals and in humans, may have been more important than pharmacokinetics and tolerability. Therefore, such pharmacodynamic data obtained early in the development of a drug may have considerable value in later stages when the benefit–risk ratio of a new compound is finally determined.

When epidemiological data show some sort of increased hazard for drugs on the market, the absence of mechanistic data to show that the drug is not responsible for the adverse event means that the precautionary principles underlying drug regulation allow little else than discontinuation. The presence of mechanistic data may lead to more careful development of the drug in a more select group of patients rather than immediate marketing in large populations. In such a way the pharmacological findings can be studied in detail in the clinic. Such an approach costs time and money but will be more economical in the end when applied to the right (high uncertainty) projects.

Dangerous lack of pharmacology

When a prototypical drug is developed in a standard manner unexpected events may be more likely to occur. The CD28 agonist TGN1412 (developed by TeGenero Immuno Therapeutics) is a good example of a prototypical new drug, resulting from increasing biological knowledge in immunology and the physiology of T cell activation. The link between the molecular effect of the drug on a T cell and the expected clinical effect was not proved and additionally there were no validated biomarkers for this. TGN1412 caused serious damage to six healthy volunteers in a first-in-human trial[33].

TGN1412 was developed in a standard manner with little consideration given to its prototypical nature. Molecular, cellular and whole organism studies were done in several species, but there was little done to connect the findings in a conceptual manner (FIG. 5) in the investigator's brochure of the drug. For example, the amino acid sequence of the receptor that was available in the public databases at the time of the protocol assessment was not homologous between the cynomolgus monkey and humans. This was later shown to be erroneous as the amino acid sequence of the receptor are homologous between the cynomolgus monkey and humans, but the structure of the receptor was only made public after the clinical trial was done and no questions were raised about the lack of homology by either the regulatory agency or the ethics committee overseeing the trial.

Additionally, no *ex vivo* experiments showed similar functional T cell responses in cynomolgus monkeys and humans. In the repeated dose toxicology experiments in monkeys, pro-inflammatory cytokines were

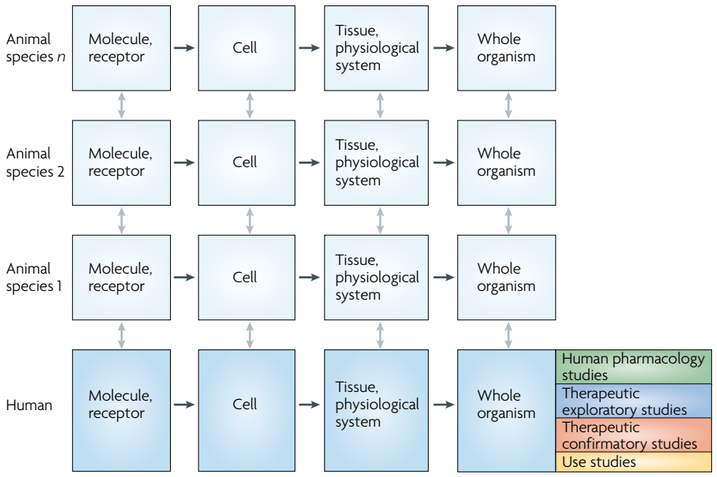


Figure 5 | **Translational drug development.** Black single headed arrows are translational connectors, such as pharmacokinetic–pharmacodynamic models or systems biology models, that allow the quantification of the link between different biological processes. Grey double-ended arrows represent linkage markers. Rather than a linear process a cyclical path can be traced through the process in any direction (in contrast to the usual situation shown in FIG. 3).

measured and, in fact, increased slightly. However, the cytokines interleukin-10 and interferon-γ that are produced by regulatory T cells — the target cell population to be stimulated and increased — were not measured as a primary pharmacodynamic measure. The results from the preclinical tests were presented to the regulatory authority in a simple format without any attempt to integrate the findings obtained in animals, human tissue and cell culture, using concentration–effect modelling (FIG. 5).

The regulatory authority responded with an approval for clinical testing that contained large unchanged sections of the original application. The protocol for this study had just the tolerability and the safety of the compound as its primary objective; T cell and cytokine measurements were considered secondary, unspecified and not included as stopping rules or used as linkage markers. The way the first dose was chosen is exemplified in FIG. 4a.

In toxicological testing, TGN1412 was given to an animal species in which the drug had little effect and as pharmacological effects are not normally included in toxicology experiments the absence of the intended effect remained undetected. Additional data from mice equipped with a human immune system, which showed the human pharmacology of the drug in human tissue and physiology (and incidentally showed the severe depletion of T cells that was seen in the volunteers) was not included in the information submitted to the regulatory authorities[34]. The calculated starting dose was too high as it was based on the NOAEL approach only, disregarding the pharmacological and immunological effects of the protein and its receptor occupancy.

If a more integrated approach had been chosen for this prototypical compound, the first and most obvious link between concentration and effect on T cells could have been made without performing any additional experiments. A calculation of receptor occupancy of the human receptor, in combination with simple pharmacokinetics, showed that the first dose of the drug resulted in >90% receptor occupancy. This was only done after the adverse events occurred. A logical subsequent experiment would then have been an *in vitro* stimulation test on different populations of human lymphocytes, in comparison with, for example, the lymphocytes of the cynomolgus monkey, but this was not done. The investigating committee[35] that dealt with the clinical trial eventually performed additional experiments in human and primate cells and in primate models, thus providing further linkage markers albeit too late for the subjects who suffered from severe side effects.

Failure to recognize that TGN1412 was not a standard compound may have been the overall cause for the tragic sequel for the subjects in this trial. The trial of TGN1412 is a reminder that standard development of a prototype has the potential to seriously harm humans and destroy a prototypical compound that may still be of important therapeutic value.

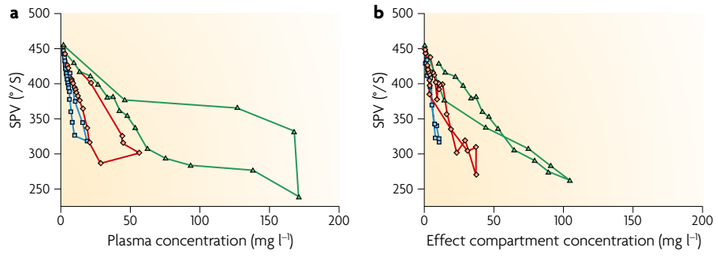


Figure 6 | **A first-in-human pharmacology experiment.** Average effects on a physiological measure of attention, calculated as the saccadic peak velocity (SPV), in response to concentrations of an experimental benzodiazepine Ro 48–8684, measured the plasma concentration (**a**) and the effect compartment concentration (brain) (**b**) in two doses (represented by blue squares and red diamonds) and the positive control midazolam (represented by green triangles). These data produce a dose–response curve for the desired effect in humans and immediately lead to a range of clinically active doses. The data were obtained during the first administration to humans with pharmacological measures as its primary objective. Figure is reproduced, with permission, from REF. 46 © (1997) John Wiley & Sons.

Sensible scientific objectives

There is no doubt that knowledge about the tolerability and safety of a drug is paramount. However, I contend that it is impossible to estimate this reliably in early development as the only parameter to determine go/no-go decisions about development. The fact that a compound is well tolerated is of importance, but only if this occurs at a dose or concentration level that is likely to produce pharmacological effects and even then this may not be generally true as the duration of treatment or the condition of the subjects may hide important tolerability problems in other populations. Conversely, non-tolerance at a dose that exceeds the effective dose by far (as was the case for TGN1412) is only relevant for the determination of a safety range or a therapeutic index, but this can only be done with considerable risk for the subject. Especially when the drug has a large safety margin, unrealistically high doses have to be given to reach the tolerability level.

If tolerability and safety in isolation are not sensible primary objectives for an early study, what are? It is plausible that a therapeutic dose of any medicine is in fairly close relation to a dose (or plasma concentration) that causes its intended pharmacological or physiological effect. Therefore, if a good measure of the pharmacological action of a drug can be included early in prototypical development, this will be more useful in determining the range of doses that are likely to be active. The results can then also be used to confirm the minimally anticipated biologically effective level from the animal experiments and to confirm and validate pharmacokinetic–pharmacodynamic models.

In addition, the early discovery of the potentially irrelevant effects of a drug at unrealistically high doses may produce unnecessary concerns about a prototypical drug. Importantly, the safety of the subjects in the clinical trial is much less a concern if there is no need to reach levels at which clinical tolerability is compromised.

The concept of CD28 superagonism — that is produced by TGN1412 — is potentially of great value in immunology and may well be explored again in the future. The TGN1412 trial showed an old principle stated by the sixteenth century Swiss chemist Paracelsus, that everything becomes toxic at a sufficiently high dose.

Translational development

Assuming that animal pharmacological data are already available, it would seem plausible to set up the same sequence of molecule to cell to tissue to organism for humans (FIG. 5). In this schematic view, the translational development data are systematically connected in a knowledge management system in which as many links between the different items are established. Using techniques such as pharmacokinetic–pharmacodynamic modelling or systems biology, also allows quantitative links to be established that facilitates the prediction of effects and pharmacokinetics across species. Such a system is not unidirectional anymore and allows a translational path to be traced forwards and backwards to learn and subsequently to confirm findings in another species or situation.

At the Centre for Human Drug Research, Leiden, the Netherlands, such experiments are performed regularly and FIG. 6 shows an example of data obtained from a first-in-human pharmacology experiment in which intensive pharmacodynamic data were obtained in order to get immediate quantitative information about the drug action of a new rapidly acting benzodiazepine. Additionally, its concentration–effect relationship could be determined by comparing it with a relevant positive control. Such data from intensive first-in-human experiments have now been performed at the centre with most classes of central nervous system drugs and also with anti-inflammatory drugs in asthma, diabetes and hypertension[36,37].

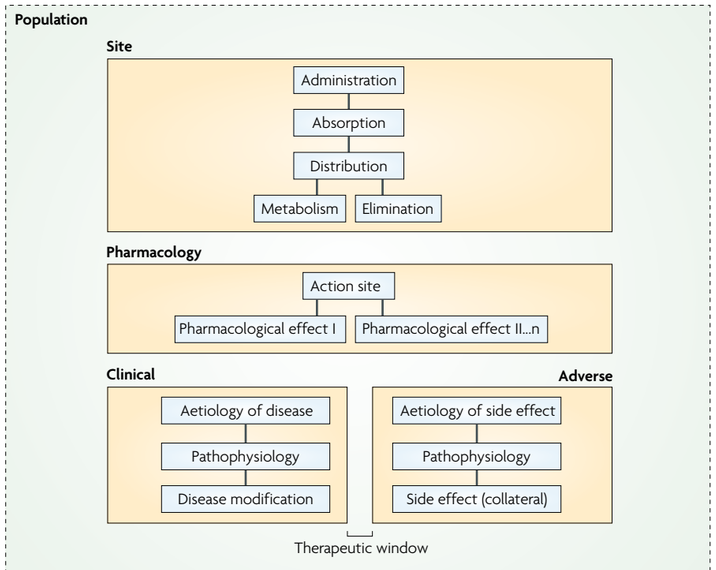


Figure 7 | **A schematic to determine the objectives using the question-based approach.** Six areas of interest can be recognized; population, site, pharmacology, clinical, adverse and therapeutic window. For example, the site group of questions deal with whether the drug can reach its site of action. Biomarkers can be pharmacokinetic measurements in blood or in other body fluids but it can also be positron emission tomography scans of the brain. Pharmacological questions are answered by the most directly related marker of activity on a receptor system or enzyme. Clinical questions attempt to study the relation between modification of pathophysiology and 'feelings, function or survival'.

Integrated translational development

If the integrative approach presented in FIG. 5 had been undertaken for TGN1412 before the compound was given to human volunteers, the findings from different animal species would have been viewed in the context of the human immune system in a scientifically cohesive manner. This may have led to adequately validated linkage markers; for example, of the effect and binding of TGN1412 to human lymphocytes. This assay could have been safely done using blood samples from the human subjects and would have led to a pharmacological determination of the dose. Moreover the assay could also have been used in different species to investigate their differences. The preclinical development of such assays would have probably directed attention to the necessity of the calculation of receptor occupancy and may have led to a considerably lower choice for the starting dose, as determined by this assay rather than the fraction of the NOAEL, and guidelines for terminating the study or modifying the dose increments would then have been dictated by blood and cell biomarker changes. This is how modern drug development for a prototypical compound should be done.

One of the reasons why this approach is not common practice is that current organizational structures are directed towards standard development; adopting a prototypical approach may require different organizational structures and training of project leaders. Collecting and displaying the research data according to a structure as indicated in FIG. 5 also have several other advantages. It would greatly assist any authority that has to review data from prototypical projects; as indicated earlier, a structured analysis and display of the risks in a first-in-human study will increase the safety of the subjects[24]; and the early data on the intensive development of drugs will show much earlier that the drug works biologically in humans. Even though the measurements of pharmacological effects are not proof of clinical principle, they are proof of pharmacological principle and this by itself may create enthusiasm for further funding and therefore value.

This is illustrated by a project with an orexin antagonist intended as a hypnotic. This antagonist was developed based on the knowledge that deficient orexinergic function leads to narcolepsy in animals and humans. However, there was no previous data proving the link between sedation and blockade of the orexin receptor, but methodology to test this was well validated in earlier studies[38]. This led to a well-coordinated sequence of studies in animal tissues and humans using a range of linkage markers of hypnosis. In the first administration to humans the effects on sleep and sedation could be established in relation to a positive control, zolpidem[39]. This led to immediate identification of the effective dose range.

This sequence of studies indicates well how early addition of information in first-in-human studies can add value by reducing uncertainty beyond the tolerability in humans. This study was also unique in that it immediately faced the comparison with existing therapies and showed potential superiority. The orexin antagonist that was developed in this modern manner was licensed out immediately after the human pharmacology studies for a considerable amount, showing the financial value of the early reduction of uncertainty.

Question-based development

The potential advantage of the traditionally four-phased approach to drug development is that it provides guidance to the planning of the clinical development for any new drug. However, it can be predicted that many of the future potential medicines will be increasingly prototypical and this means no guidance can be obtained from previous experience with similar projects. If a standardized approach will not work, what will?

Any research project or programme starts with the formulation of a set of questions and this approach has been used to design a structured system for the evaluation of new medicines[40]. Question-based drug development makes use of the logical progression of questions as shown in FIG. 7. A new drug has to reach its site of action, will affect a system by its pharmacology, thus affecting (patho)physiology and finally modifying the disease in a certain defined population. A compound may also have unwanted effects (that are also pharmacological[41]) for which the same criteria apply. Such a system can be used to design a set of research questions and to investigate whether the biomarkers and specific linkage markers for answering the questions are validated. This can be done at an early stage of the development and provides insights into what information has to be collected, as well as the methodology that has to be developed.

Essential questions that cannot be answered are a clear representation of the development risk. As stated earlier, a prototypical development project adds much more value to the product by adding information to resolve existing uncertainties rather than by reducing time to market or cost by just performing a standard trial more rapidly. There are still many standard-type drugs in development and so determining how prototypical a project is, is essential to determine the type of project management required. The question-based approach can be combined with advanced decision analysis techniques to determine the added value of obtaining information in the project versus the potential loss of time and the increased costs this may entail[40].

The next chapter of drug development

The increasing knowledge about biology has already led to an explosion of potential drug targets. These may not have led to the explosion in profitable products the pharmaceutical industry promised its shareholders but the signs of a wave of new medicines with entirely new mechanisms of action are already there[42]. Many of these mechanisms will not be in the usual realm of the pharmacologist. For example, the tenth edition of a standard pharmacology textbook[43] devotes 180 pages to the autonomic nervous system (a chief source of 'me too' products) and a meagre 28 pages to the immune system, in which many of the major advances are being made. This means that the uncertainties in many of the projects will increase and dealing with these unknowns requires a radically different approach. Training individuals who can lead these prototypical projects is perhaps the most important step to be taken[44]. Recognizing when the projects are prototypical is the next step, and this will be made considerably easier when done by specifically trained individuals. Development of methodology to deal with the uncertainties will then follow.

Determining whether such an approach would have kept tegaserod on the market is impossible, but the wave of prototypical compounds will probably grow and we need to be prepared for it through the appropriate systems of knowledge management, the investment in alternative techniques beyond counting side effects and the training of researchers to deal with the complicated information. Some of the disasters that have happened when traditional drug development was applied to innovative projects should help us in designing these properly. In doing so we would finally do justice to the simple country doctor from Shropshire who predicted it all.

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Competing interests statement

The author declares no competing financial interests.

FURTHER INFORMATION

AstraZeneca's Annual Report 2006: http://www.astrazeneca-annualreports.com/2006/astrazeneca-annual-report-20F-2006.pdf
Central Committee on Research Involving Human Subjects: http://www.ccmo.nl
Note for Guidance on Repeated Toxicity (CPMP/SWP/1042/99): http://www.ema.europa.eu/pdfs/human/swp/104299en.pdf
Author's homepage: http://www.chdr.nl

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Laura Herman was a speaker at the CHDR 25th anniversary symposium in 2013. The concept of shared value, introduced by Harvard Business School Professor Michael Porter may contain the solutions for further growth and effectiveness of research for new medicines. The collaborative models in research clusters, associations between academia and industry and the rapid emergence of small, entrepreneurial companies are all signs of new value systems that will potentially transform the research environment.

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Shared value is inherent in health technology companies.

By Michael E. Porter, Professor
Harvard Business School and Co-Founder, FSG

Pharmaceutical and medical device companies, the focus of this report, create both economic and societal value when they provide products that tackle important health problems. Not all fields have clear opportunities to create competitive advantage while simultaneously advancing such a vital societal goal as better health. However, the opportunity for these industries to create shared value is far greater.

Capitalism faces a watershed moment.

Now is the time for the private sector to demonstrate its potential for both economic growth and societal purpose. As companies create shared value by meeting social needs, the capabilities and scalability of business is unleashed on societal challenges such as the rising burden of non-communicable diseases in the developing world. Government, local health systems, and the nonprofit sector will play leadership roles in prevention and treatment. But capitalism, guided by the pursuit of shared value, will take on a greater role in addressing the global burden of disease.

CREATING SHARED VALUE

"Companies create shared value by creating economic value and societal value simultaneously. There are three distinct ways to do this: by reconceiving products and markets, redefining productivity in the value chain, and building supportive industry clusters at the company's locations."

Michael E. Porter and Mark R. Kramer, "Creating Shared Value," *Harvard Business Review*

This report follows the January 2011 release of the article "Creating Shared Value" in *Harvard Business Review.* It represents the first of a series of studies that will focus on shared value within particular sectors.[1] The report seeks to inform and inspire companies in the pharmaceutical and medical device industries, while providing insights that can assist companies in other fields create and implement shared value. We hope that this study spurs leaders from the private sector, civil society, investors, and government in new approaches to addressing health problems through new management thinking, innovations in business models, and cross-sector collaboration.

Historically, pharmaceutical and medical device companies built their businesses by serving affluent markets in North America, Europe, and Japan. In the process, they have overlooked the unmet health needs of billions of underserved patients, and with it, huge opportunities for innovation and growth.

Fortunately, there are promising signs of change. Some pharmaceutical and medical device companies are prioritizing previously underserved patients and markets. Rather than seeing efforts in assisting lower income customers as corporate social responsibility and philanthropy, companies are transforming their products, pricing, manufacturing, distribution, and marketing to profitably meet previously unmet needs. There are encouraging signs that serving these new markets can be profitable, and multiply the size of the available market.

Executive Summary

A new dynamic is changing the basis of competition in the pharmaceutical and medical device industries.

Increasingly, companies are seeing opportunities to meet the needs of underserved populations in low- and middle-income countries, where they once saw little commercial interest. This report highlights how pharmaceutical and medical device companies are **creating shared value in global health** by enhancing their competitiveness while simultaneously addressing the global burden of disease — often working in partnership with governments, funders, and nonprofit organizations.

Background

- In return for investing in risky R&D to develop revolutionary, life-saving technologies, society provides pharmaceutical and medical device firms with intellectual property protections that reward success. While this social contract has worked well for the world's richest nations, until recently, the underserved in Asia, Africa, and Latin America have generally been an afterthought. Global health advocates have called for better adapted products and lower prices, to which companies have responded. But until recently, efforts have largely been philanthropic or reputation-driven.
- In the last decade, this picture has begun to change. Developed markets are coming under pressure as traditional health systems are scrutinizing costs as never before. At the same time, R&D productivity has fallen, particularly for pharmaceutical firms. This is forcing companies to reconsider opportunities in low- and middle-income countries they may previously have overlooked. In parallel, newly recognized market opportunities are emerging around the enormous unaddressed health needs in these countries. Emerging markets could account for nearly half of worldwide revenues for pharmaceutical companies by 2012,[2] and these areas are expected to account for 75 percent of industry growth over the coming decade.[3]

The Shared Value Opportunity

- Companies create shared value in global health when they compete on the basis of improving health outcomes for the underserved. Rather than competing for market share among well-funded payers and wealthy patients, companies view their success in terms of their ability to improve health outcomes by building and serving new markets. To achieve that success, companies need to systematically and relentlessly uncover new, unmet needs, and find new and better ways to address them at scale.
- Low- and middle-income countries have vast unmet needs. The top five non-injury causes of death in 2008 claimed nearly 29 million lives in low- and middle-income countries, compared with just 6.6 million in high-income countries. Southeast Asian and African countries, in particular, face a double burden of infectious diseases and non-communicable diseases (NCDs), such as cardiovascular disease, diabetes, and cancer.
- Meeting these needs is challenging, even for sophisticated corporations. Missing skills and knowledge, limited market information, ineffective regulation, inadequate health systems, and limited funding or inability of patients to pay present firms with huge barriers to entry. To overcome these barriers, companies are investing in three levels of shared value (see Figure 1).
- Efforts to create shared value across the three levels are mutually reinforcing. Productive and lower-cost value chains are essential to introducing redesigned product portfolios to underserved markets. Strong clusters can enable firms to serve population segments that were previously out of reach, and can open up new, lower-cost manufacturing and distribution options. Leading firms are beginning to design multi-level approaches to harness this multiplier effect, though the right combination will be unique to a particular company and market.
- Stakeholders and shareholders are warming to shared value. Global health stakeholders desire a move away from charity to more sustainable and scalable ways to provide drugs, vaccines, and medical devices to patients in underserved markets. And these stakeholders want to partner — in a recent survey, 79 percent of nonprofit organizations reported that pharmaceutical and medical device companies are essential partners in the effort to achieve their missions.[4] Mainstream investors are adopting a wait-and-see attitude to company engagement in low- and middle-income countries. More socially-minded investors and analysts are paying increasing attention to companies reaching the underserved.
- Shared value cannot address all global health needs. Systemic market failures exist in health technology, notably around neglected diseases, where needed products and services are not being developed or delivered on a commercial basis due to the inability of patients to pay. A shared value frontier defines the boundary of such failures.
- However, companies are innovating to serve patients at the shared value frontier, where health systems are notably deficient or patients lack the ability to pay. As local complexities increase, companies are employing sophisticated combinations of shared value approaches. In the longer term, there is good evidence to believe that some companies will expand the shared value frontier further into poorer populations.
- Corporate philanthropy and external funders, such as governments and foundations, can also bridge the shared value frontier. Corporate philanthropy can accelerate existing shared value initiatives — often through strengthening health systems — or incubate new projects in locations where companies do not have commercial operations. Governments and private funders also offer incentives that reduce risk for investments in R&D efforts or establish commitments for future drug or vaccine purchases.

Figure 1: Levels of Shared Value Creation for Pharmaceutical and Medical Device Companies

1 Reconceiving Products and Markets	2 Redefining Productivity in the Value Chain	3 Enabling Local Cluster Development
• R&D for drugs, vaccines, and devices that fill unmet health needs	• Collaborative and homegrown R&D to reduce cost and risk	• Behavior-change campaigns to increase the sophistication of demand for health care
• Adaptation of existing products to reduce complexity and cost	• Efficient, local supply chains and manufacturing to reduce production costs	• Health system strengthening to enable delivery of needed products and services
• Tailored product offerings to meet local market conditions	• Locally-adapted sales and distribution to penetrate new markets and better meet patient needs	• Advocacy and capacity building to strengthen policy and the regulatory environment

Implementing Shared Value for Global Health

Common success factors are emerging among companies as they implement shared value. Leading companies are following five principles:

- **Focused and determined leadership at the CEO and country levels.** Companies that excel at shared value have CEOs and country-level managers who bring a compelling vision and personal involvement to expansion efforts in low- and middle-income markets. Without leadership, pharmaceutical and medical device companies stumble and resort to more traditional, charity-led engagement with patients in low- and middle-income countries.
- **A culture of innovation and learning reflected in structures and incentives.** Cross-functional teams can help to coalesce, prioritize, and coordinate shared value approaches that straddle R&D, government affairs, and marketing. Companies have also created separate social innovation units that directly manage shared value initiatives.
- **New approaches to measurement that track the link between business value and improved patient lives.** Such metrics offer companies a way to understand what works to create shared value, and allows them to assess the potential of new investments, to allocate resources, and to set relevant incentives. While few companies have developed robust systems to measure shared value, early adopters are starting to use such information to make key management decisions, and are seeing improved performance as a result.
- **New skills in identifying and acting on unmet health needs.** To penetrate new markets, companies require employees with on-the-ground knowledge of health needs among underserved patients, an ability to translate needs into business strategy, and strong stakeholder-engagement capabilities.
- **New partnerships for shared value insights and implementation.** Companies are looking to a new set of partners to help with shared value strategy-setting and specific competencies in adapting products, improving productivity and cost effectiveness, and strengthening the competitive context. Many of these partners are nonprofits, which marks a shift from prior roles as corporate philanthropic grantees.

Catalyzing Greater Shared Value for Global Health

The following recommendations for companies and stakeholders can catalyze greater experimentation in shared value for the benefit of companies, patients, and health systems.

Recommendations for Companies

- *Shift from defensive to affirmative engagement with patients in low- and middle-income countries.* Companies should be transparent with global stakeholders about their ambitions in low- and middle-income countries. Specific shared value approaches, motivated by profit, can be articulated for the benefit of the global health field. Where shared value approaches are not presently feasible, companies can explain the role of their philanthropic contributions and the intentions of partnerships with government and private funders.
- *Innovate and capture knowledge on health product delivery.* As companies learn more about how to market drugs, vaccines, and medical devices to the hard-to-reach and poorly-served populations, lessons should be shared, within the limits of competitive confidentiality. Promising multi-sector models for sharing best practices on health product distribution and disease awareness-building are emerging.
- *Experiment with shared value measurement to spur learning and innovation.* Pharmaceutical and medical device companies should be in a position to lead other industries on measuring shared value, due to the inherent alignment between the increased sales of their life-enhancing products and meeting patient health needs. Companies should set, specific, forward-looking targets for populations, behavior changes, health system strengthening and disease indicators, and should measure progress towards them.
- *Invest early to gain first-mover advantage.* Companies that invest ahead of their rivals, such as GlaxoSmithKline in India and Novo Nordisk in China, find themselves with a sizable competitive advantage as new markets develop and mature.

Recommendations for Global Health Stakeholders

- Context-setting institutions, such as governments and civil society, can monitor the results of shared value initiatives, including patient outcomes and health system improvements. Specifically, advocacy-oriented organizations have a role to play in ensuring that health technology companies develop strategies to expand access to poorer patients at the frontier of shared value in Africa and Asia. Organizations that provide information and insight on unmet health needs can stimulate more immediate shared value opportunities through patient research, value chain analysis, and health system auditing. Organizations that partner with companies to implement shared value strategies can be more proactive in offering their services. Lastly, funders can incentivize the private sector to scale-up delivery of health products to patients in remote locations or where health systems are particularly deficient.

PART THREE

Architecture

The history of the new eye-catching building for CHDR can serve as a metaphor for the organisation itself. Almost by serendipity, the CHDR board of directors decided to claim a lot adjacent to the building they were in at the time. It turned out to be an interesting piece of land, as others wanted to lay claims on it just a week after. But it also proved to be a complicated niche, requiring much creativity from the architects and support from the local municipality to turn it into its current success. The result is a transparent, lucid building with an architecture that borders on choreography. Now that it's there, it looks so easy. For those who like to know how it was done, the architects unveil some of their secrets in the following pages.

The architecture of CHDR II

GFA
6,961 m²
Design
architectenbureau cepezed bv, delft
Structural engineer
Smit Westerman | Gouda
Installations and utilities
Deerns, Rijswijk
Fire engineering
Efectis, Rijswijk
Interior design
Fokkema & partners, Delft
architectenbureau cepezed bv, delft
Building physics
B.B.A. Binnenmilieu bv, Rotterdam
Management
ID – bouwen van architectuur, delft
Contractor
Du Prie, bouw en ontwikkeling, Leiden

In the mid-1990s, CEPEZED designed an eye-catching company building for the Centre for Human Drug Research (CHDR), as well as various accommodations for other pharmaceutical companies at neighbouring sites. Despite the construction of an extension for CHDR around 2000, the firm began to burst at the seams.

Likely because of its restricted size and irregular outline, the very last building site in this area of the Leiden Bio Science Park, right next to the existing CHDR, was still available. Therefore, CHDR asked CEPEZED to investigate the possibilities of a new, state-of-the-art research building here, which should be fit for different tenants and support a multidisciplinary exchange of ideas.

The small and idiosyncratic site begged for a multi-layered design, resulting in a building volume higher than construction projects erected in this district thus far. The municipality and urban designers welcomed the dense use of the terrain, as well as the creation of a modest but recognisable landmark. Since CHDR's core business, the testing of medicines, must take place in strictly controlled conditions and the testees can't leave the building during the sometimes lengthy procedure, the ambition was to create a great diversity of places for a wide variety of spatial experiences, and thus avoid tedium and monotony. Among the building's features are a roof patio, living rooms with small kitchens, and a canteen with large sliding facades that open to become a huge balcony. It is also outfitted with advanced research rooms; laboratories; meeting spaces; and a flexible, innovative office layout.

The new building consists of a volume measuring 22.5 by 34 metres, with eight layers above ground and a subterranean car park – the first in the area. Parking also occurs partly on the surrounding terrain and at surface level within the contours of the building. Thus, only the entrance and auditorium areas at the front touch the ground.

From front to back, the building is divided into three unequal strips. The foremost strip along the Zernikedreef contains the entrance, the reception desk, and a modest auditorium on the ground floor. Above these are the meeting rooms and offices, as well as the testing areas and a roof garden with greenery.

The central strip is an amenity zone, with toilets, two completely transparent lifts, and two linked cascade staircases that also function as emergency exits. In the case of fire, an automatically-descending, fire-resistant curtain separates the staircases. The open and spatial quality of the usually closed double safety staircases not only provides daylight deep in the building, but also stimulates interaction between researchers, visitors, testing people, and clients.

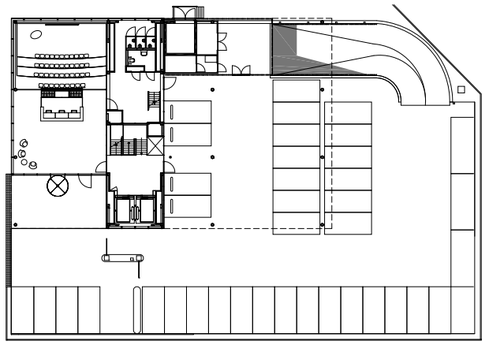
The strip at the rear contains the canteen, with fronts that can largely be opened, a high-care zone, a research laboratory with a pharmacy connected to it, and various storage and freeze facilities. The top floor consists of bedrooms for long-term stays and a corresponding living room adjoining the roof garden.

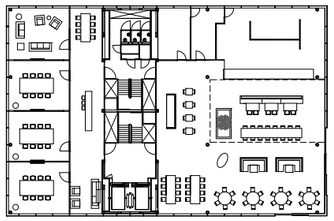
The load-bearing construction consists of a slender steel skeleton combined with hollow-core slab floors. The prefabricated hollow-core slab floors have been positioned in such a way that extra structurally integrated space has been created for all ducts, pipes, and cabling, thus rendering extra free space within the building volume. The integrated wiring, cabling, and piping are fed through four slender shafts in the central facility zone. To realise this complex unification, use has been made of an integral Building Information Model, by means of which the various consultants were able to efficiently dovetail their designs.

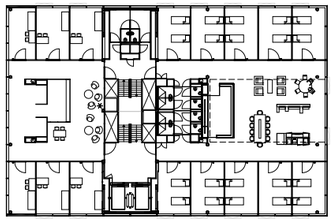
The façades have been implemented fully flush: on the north side, they are made entirely of glass, thus providing spectacular views of the surroundings and opening the building towards the street. The other, sun-oriented facades feature horizontal articulation of alternating strip windows equipped with sections that can be opened, and sandwich panels with a white enamelled glass exterior plate.

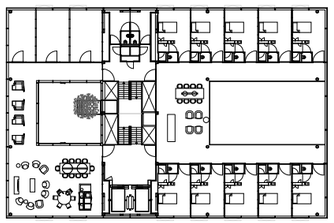
While the previous CHDR building was cloaked in dark perforated metal, the new CHDR building is clad in pure white, shiny, enamelled glass, a durable and sustainable material. A solar panel heats the boiler water. For heating and cooling, the building is linked to a district heating system that covers the entire business park, which, in turn, is connected to a geothermal heat storage system.

Through skylights and the glass in the facades, the building is flooded with daylight, providing a healthy and inspiring working environment for CHDR and the new tenants. The Leiden municipality designated the previous CHDR building as a monument of contemporary architecture. Providing an inspiring learning, testing, and working environment and fit for an international client base, the new construction will likely prove to be a lasting facility as well.







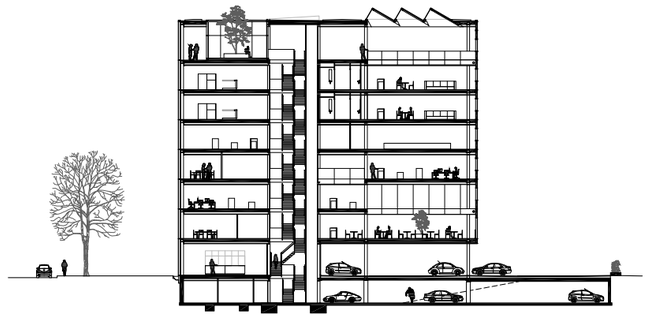


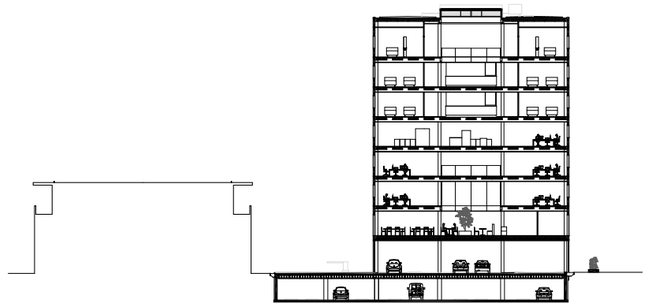
Floor plans of various storeys
Ground floor with the entrance on the north side (left part of photo), the entrance hall with reception desk, and the auditorium. In the centre: the strip with the lifts, staircase, sanitary units and shafts. On the south side (right), the parking lot at ground-floor level and the embankment with the underlying parking facilities.

The first storey with diverse meeting rooms with, on the north side, circulation and access area at the front. On the south side, we see the kitchen with the restaurant and the glass façade, which can be largely opened, at the south-west corner (below right).

The sixth storey with the blood-sample desk in the centre on the north side (left) and, on either side of this, the examination rooms. To the right of the zone with lifts, staircases and shafts are the patients' rooms with the overnight rooms along the east and west façades (above and below), with the sanitary facilities and communal room in the middle.

The seventh story with, on the north side (left), the in-house roof garden with the adjoining communal room and, next to the central zone, even more patient rooms along the east and west façades (above and below) with a spacious void in the centre.

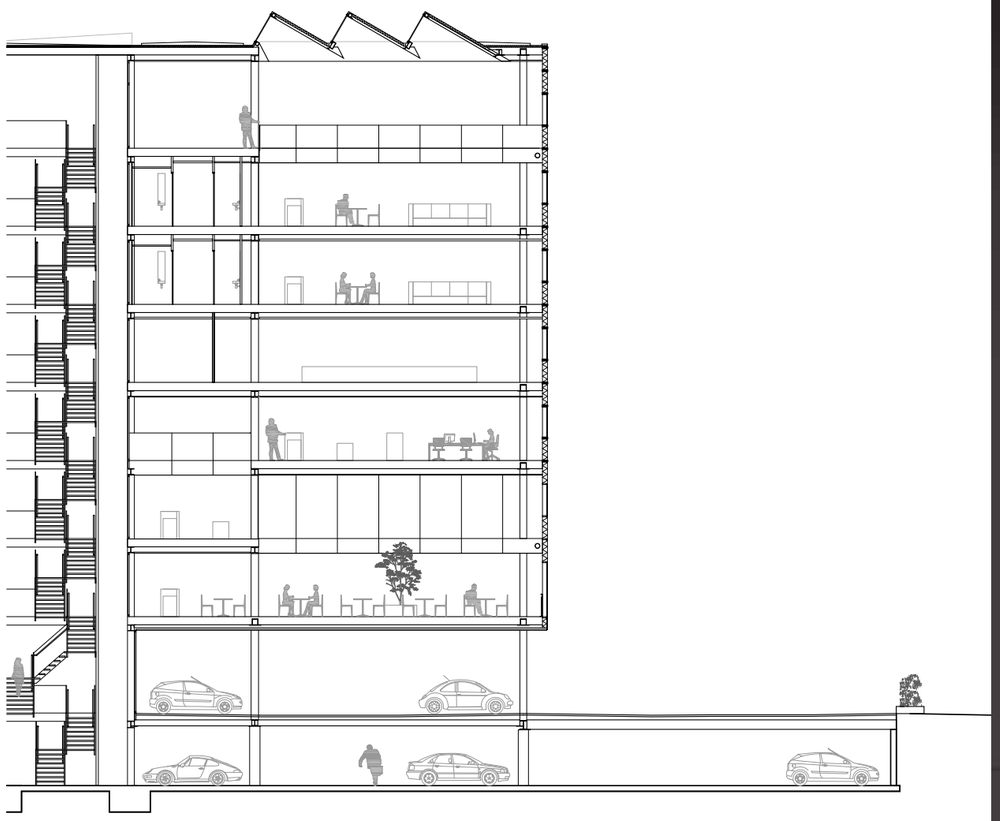




View to the west
A horizontal articulation above the car parking facility at ground level and a partly double-height, transparent plinth. The façade surface is completely flush with the parts tåhat can be opened in the transparent strips.

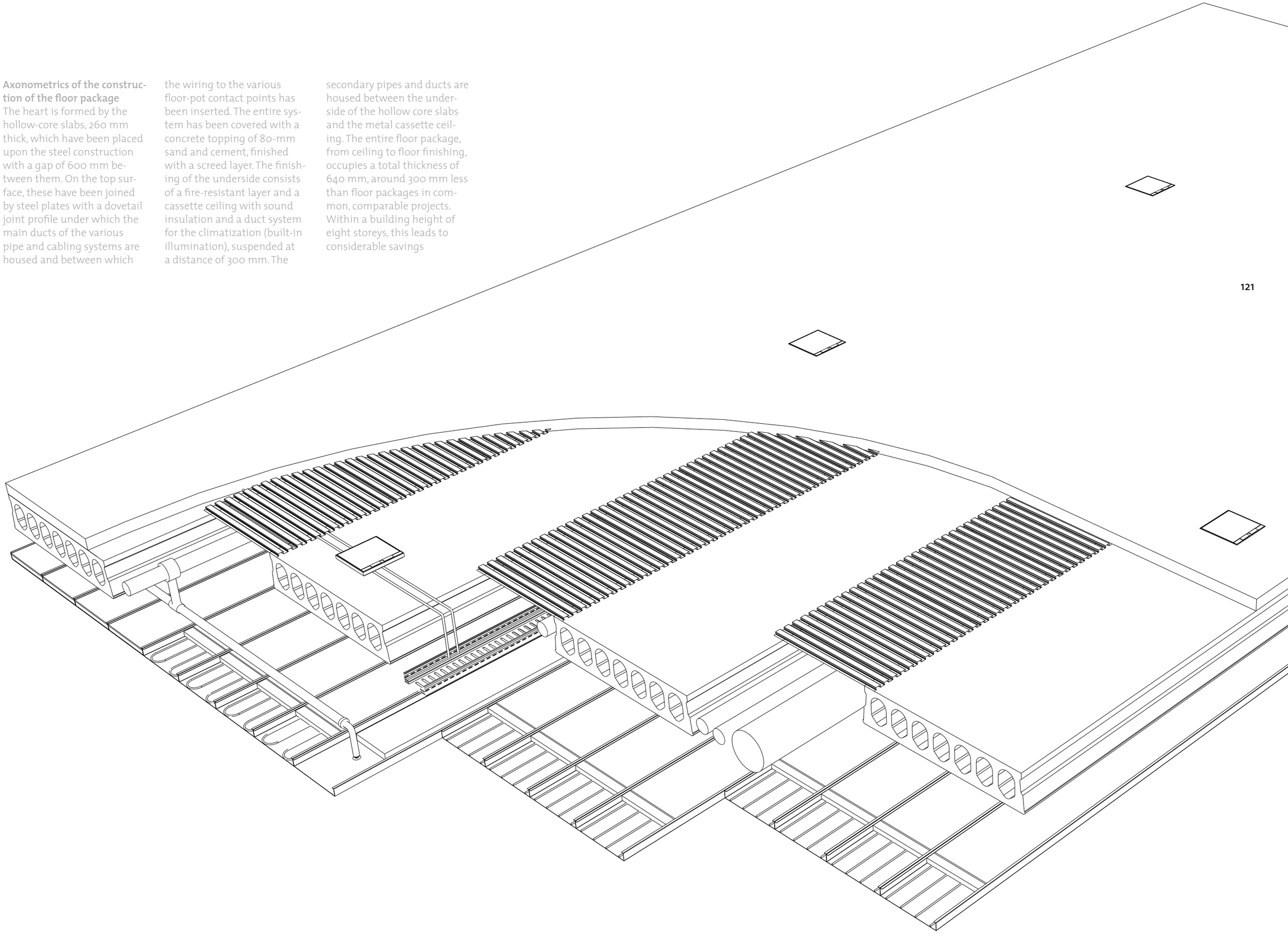
Longitudinal section
In the middle: the stabilizing zone with the lifts, staircases, shafts and sanitary facilities, among other things. On the north side (left), the façade is made entirely of glass; the more operational functions are largely housed here. On the south side (right), there is the canteen, with a façade that can be opened. The upper floors accommodate the patients' rooms. Right at the top there is a sawtooth roof with an underlying void.

Cross-section of the southern zone
On the far left (west side), there is the contour of the former CHDR building, which was also designed by cepezed. Above, in the middle, we see the sawtooth roof with its underlying void and the patients' rooms on either side. On the lower level there are the car-parking floors, the canteen and various office functions. An exceptional feature of the floors is their composition of hollow-core slabs that have been placed at a slight distance from one another and are linked by steel plates and a structural concrete topping. Space for the main routes of the various pipe and duct systems has thus been created in the intermediate hollows.



Fragment
On the far left: the stabilizing zone with the lifts, staircases, shafts and sanitary facilities. Adjoining, from bottom to top: the car-parking facilities, the double-height canteen, several office floors and, at the top, the storeys for the patients' rooms. On the far right: the horizontal façade articulation and, right at the top, the sawtooth roof above a void. The glass of the sawtooth roofs is oriented toward light from the north, while the south-oriented upright surfaces are equipped with collectors for a solar water heater.

Axonometrics of the construction of the floor package
The heart is formed by the hollow-core slabs, 260 mm thick, which have been placed upon the steel construction with a gap of 600 mm between them. On the top surface, these have been joined by steel plates with a dovetail joint profile under which the main ducts of the various pipe and cabling systems are housed and between which the wiring to the various floor-pot contact points has been inserted. The entire system has been covered with a concrete topping of 80-mm sand and cement, finished with a screed layer. The finishing of the underside consists of a fire-resistant layer and a cassette ceiling with sound insulation and a duct system for the climatization (built-in illumination), suspended at a distance of 300 mm. The secondary pipes and ducts are housed between the underside of the hollow core slabs and the metal cassette ceiling. The entire floor package, from ceiling to floor finishing, occupies a total thickness of 640 mm, around 300 mm less than floor packages in common, comparable projects. Within a building height of eight storeys, this leads to considerable savings




Onderzoek
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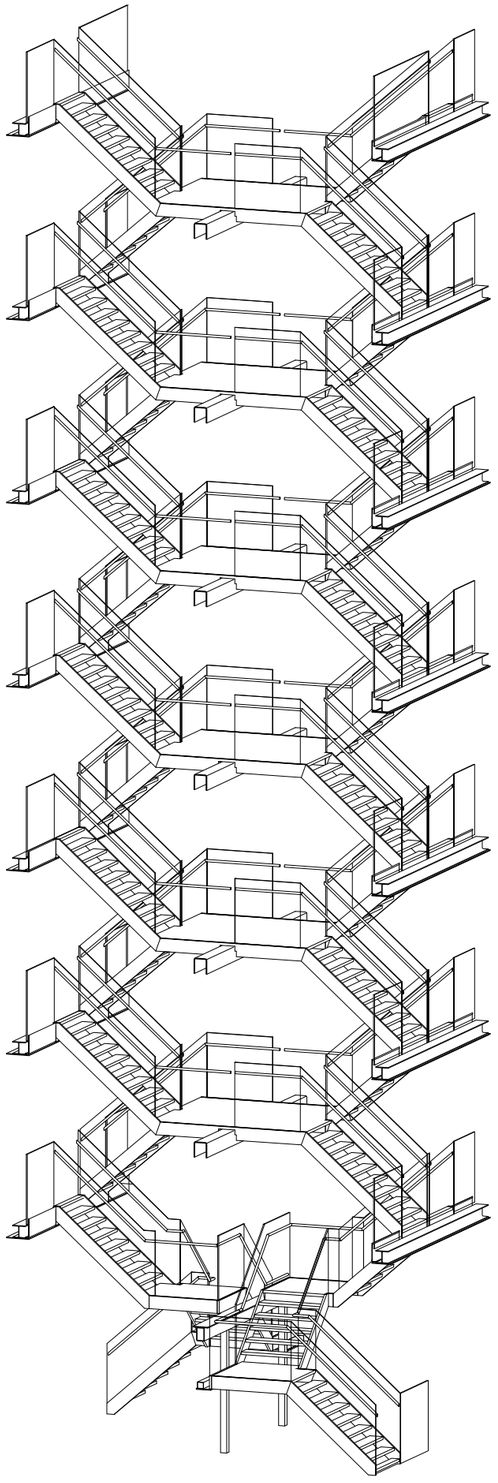
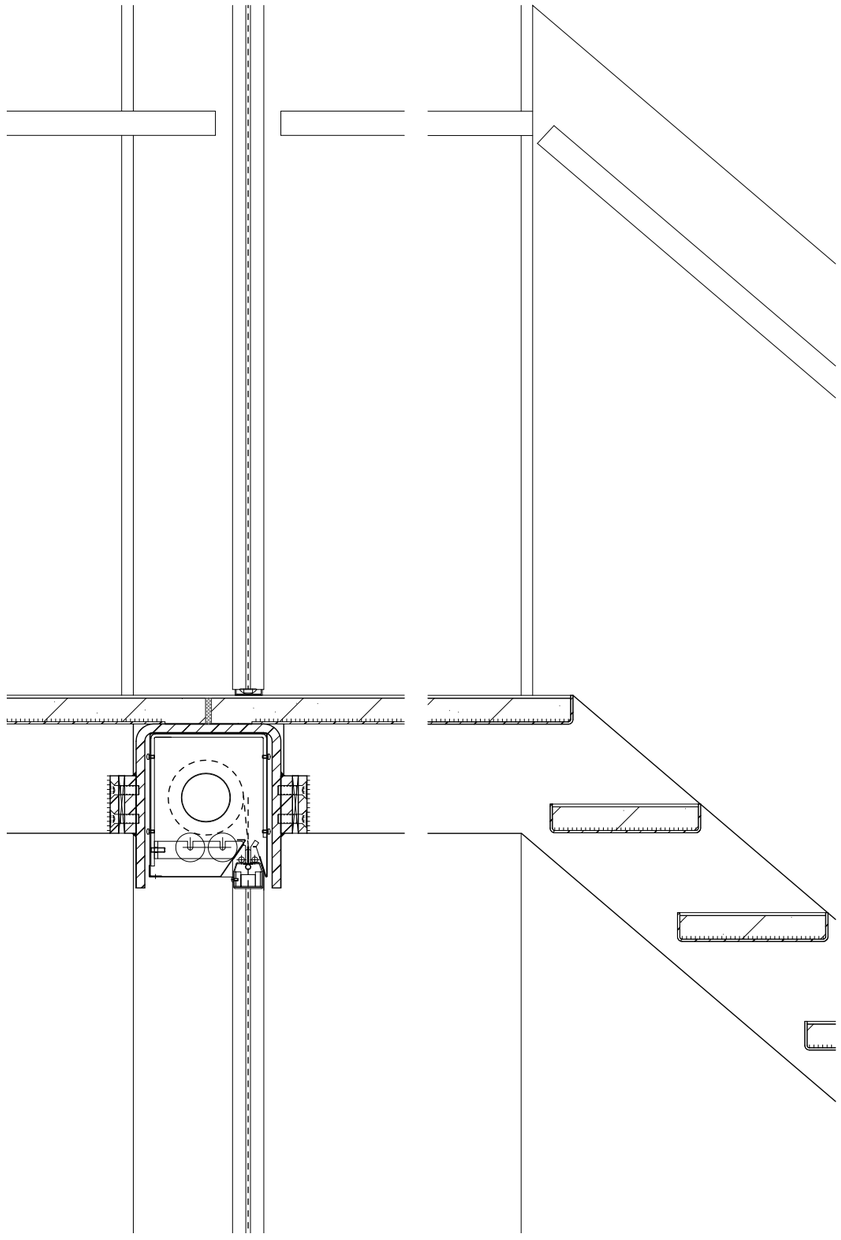
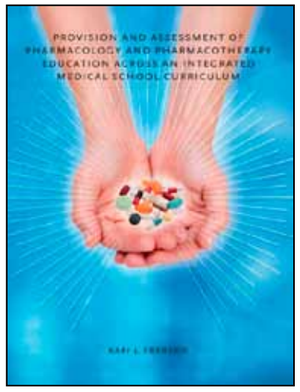
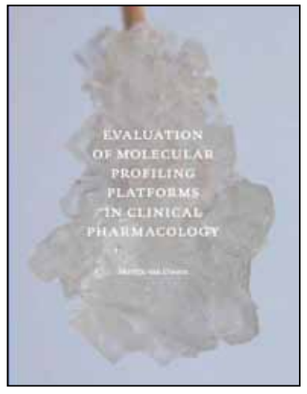


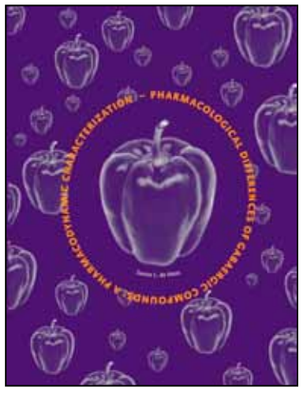


Fragment
Three-dimensional drawing of the cascade stairs in the stabilizing central zone of the building. The stairs form a connecting element between the various storeys in both a physical and a social sense. In the case of fire occurring, firescreens descend automatically, separating the two staircase zones so that there is always a safe emergency exit available. The firescreens are integrated in the UNP profiles of the steel construction. The lighting of the staircase is also integrated into the stringers.

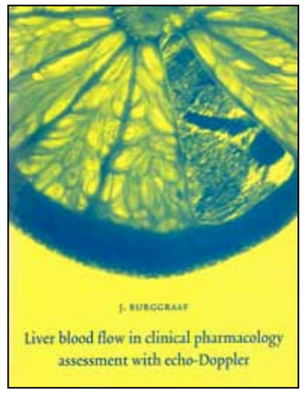
Caroline de Lint is the house graphical designer of CHDR and has designed all the front covers and typography of the CHDR PhD theses. The PhD fellows are traditionally allowed to give their preferences. This has created a varied, but related family of visual styles for a varied but related body of science!


PROVISION AND ASSESSMENT OF PHARMACOLOGY AND PHARMACOTHERAPY EDUCATION ACROSS AN INTEGRATED MEDICAL SCHOOL CURRICULUM


EVALUATION OF MOLECULAR PROFILING PLATFORMS IN CLINICAL PHARMACOLOGY


PHARMACOLOGICAL DIFFERENCES OF CARDIAC COMPOUNDS – PHARMACODYNAMIC CHARACTERIZATION –


MINIMALLY INVASIVE METHODOLOGY FOR PHARMACOLOGICAL RESEARCH INVOLVING CHILDREN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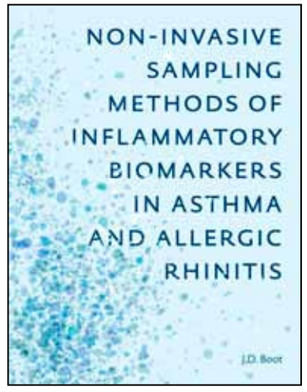
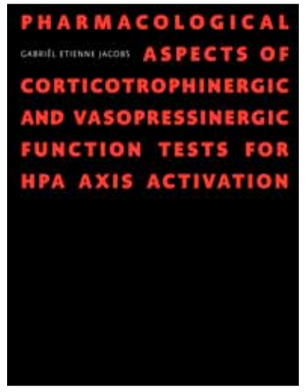
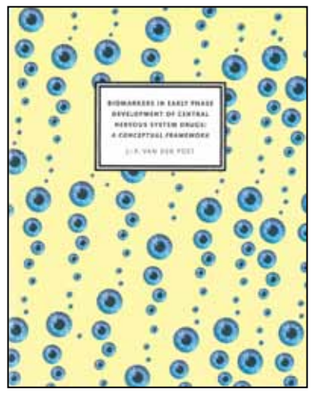
Liver blood flow in clinical pharmacology assessment with echo-Doppler


NON-INVASIVE SAMPLING METHODS OF INFLAMMATORY BIOMARKERS IN ASTHMA AND ALLERGIC RHINITIS
J.D. Boot

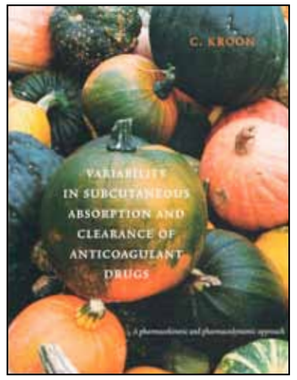

PHARMACOLOGICAL ASPECTS OF CORTICOTROPHINERGIC AND VASOPRESSINERGIC FUNCTION TESTS FOR HPA AXIS ACTIVATION


VARIABILITY IN SUBCUTANEOUS ABSORPTION AND CLEARANCE OF ANTICOAGULANT DRUGS

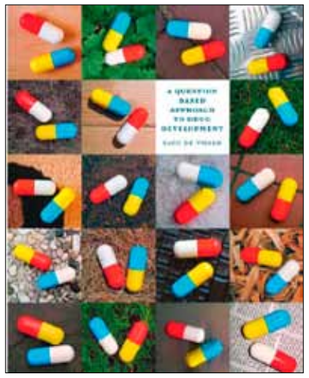

BIOMARKERS IN EARLY PHASE DEVELOPMENT OF CENTRAL NERVOUS SYSTEM DRUGS: A CONCEPTUAL FRAMEWORK

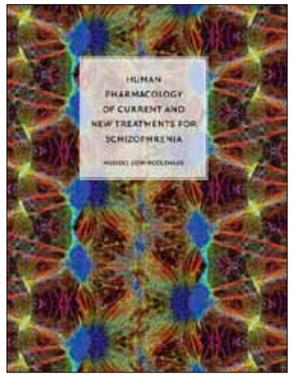

ENDOTHELIAL FUNCTION
DETERMINED FROM SYSTEMIC
PLASMA CONCENTRATIONS
RELEASE OF TISSUE FACTOR
PATHWAY INHIBITOR AND
BINDING OF TISSUE
PLASMINOGEN ACTIVATOR


Dexamethasone in ophthalmology
olga weijters

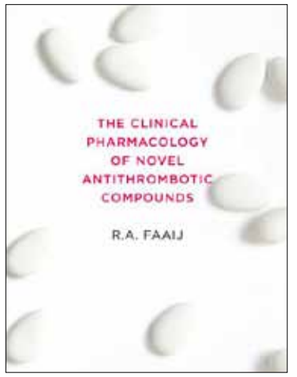

C. KROON
VARIABILITY IN SUBCUTANEOUS ABSORPTION AND CLEARANCE OF ANTICOAGULANT DRUGS


CLINICAL TARGET VALIDATION FOR A NON-PEPTIDE MOTILIN RECEPTOR ANTAGONIST

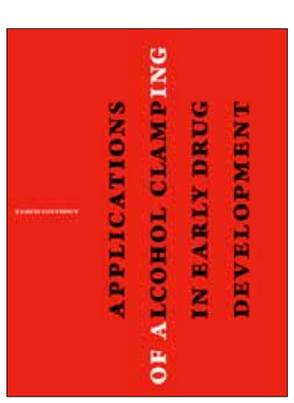


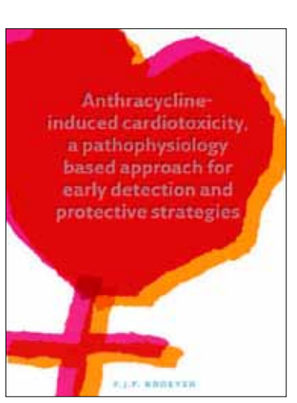

HUMAN PHARMACOLOGY OF CURRENT AND NEW TREATMENTS FOR SCHIZOPHRENIA


PHARMACOLOGICAL ASPECTS OF CHALLENGE TESTS OF THE SEROTONERGIC SYSTEM OF THE BRAIN


THE CLINICAL PHARMACOLOGY OF NOVEL ANTITHROMBOTIC COMPOUNDS
R.A. FAAIJ


BIOMARKERS IN EARLY PHASE DEVELOPMENT OF CENTRAL NERVOUS SYSTEM DRUGS: A CONCEPTUAL FRAMEWORK


APPLICATIONS OF ALCOHOL CLAMPING IN EARLY DRUG DEVELOPMENT


Anthracycline-induced cardiotoxicity, a pathophysiology based approach for early detection and protective strategies

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