

COOPERATION BETWEEN UNIVERSITIES AND PHARMACEUTICAL INDUSTRY

Proceedings of a symposium organised by the Academy Committee for Chemistry and the Council for Medical Sciences of the Royal Netherlands Academy of Arts and Sciences, the Netherlands on October 20, 2004

Royal Netherlands Academy of Arts and Sciences

# **Cooperation between universities and pharmaceutical industry**

NEW OPPORTUNITIES IN DRUG RESEARCH?

Amsterdam, November 2005

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
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# Foreword

Pharmaceutical research, nowadays, is taking place in a complex arena. The powerful, research-intensive pharmaceutical industry is forced to acknowledge that fewer new drugs are being brought onto the market at spiralling costs. Industry realises that the need for fundamental knowledge is greater than ever, but also that the complex regulations governing vital clinical research and the cost of that research are causing staggering problems. Optimal cooperation between universities and the pharmaceutical industry offers great opportunities at all stages of the drug development process. This cooperation was the theme of a symposium organised by the Academy Committee for Chemistry and the Council for Medical Sciences of the Royal Netherlands Academy of Arts and Sciences (KNAW).

This report contains the proceedings of the symposium, and the organisers have added a set of recommendations based on discussions held during the event. These recommendations not only cover cooperation in research and education, but also deal with the regulations governing drug development, the organisation of research, the protection of knowledge and entrepreneurship.

The Dutch government has recently decided to contribute a large amount of money (€130 million) to help and fund a Top Institute Pharma, which is to be established soon. The Board of the Royal Netherlands Academy of Arts and Sciences feels that the recommendations in these proceedings may aid to set up this centre of excellence. The Board of the KNAW would like to add a few comments. One is to keep in mind the importance of basic research into fundamental cellular processes, which is a major strength of Dutch scientific biomedical research. This research stimulates the development of original ideas, which may lead to new drugs. The Academy considers fundamental research at cellular level to be of paramount importance, not in the least because it is a source of insight into the molecular and cellular basis of specific diseases. In addition, the favourable conditions for patient-oriented clinical research, another area of strength in Dutch research, should be exploited to a greater extent in this cooperation between universities and industry.

Further efforts to strengthen cooperation between universities and industry are of utmost importance, with mutual understanding and respect. This also means that universities and university medical centres should not become business centres. Still, however, teaching programmes may give greater emphasis to business skills and recognise the importance of protecting knowledge properly. Such measures and those directed to implementation may lead to optimum use of research results.

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# Content

Introduction	9
Summary	11
Recommendations	15
<i>Academic research in the pharmaceutical sciences: the pre-clinical phase</i>	
Daan Crommelin	17
<i>Oncology drug discovery: cooperation between academic institutions and industry</i>	
David Schenkein	21
<i>Clinical drug development in oncology</i>	
Jaap Verweij	27
<i>Drug research from an academic perspective</i>	
Sander van Deventer	31
<i>Universities and industry: a new future together?</i>	
Werner Cautreels	35
<i>Entrepreneurship at universities</i>	
Menno Horning	39
<i>The Drug Research Academy – a Danish case study</i>	
Sven Frøkjaer	45
Summary discussion workshop 1 (in Dutch)	49
Summary discussion workshop 2 (in Dutch)	53
Summary discussion workshop 3 (in Dutch)	56
Summary discussion workshop 4 (in Dutch)	59
Symposium programme	62
List of authors	63
Organising committee	63
Abbreviations	64





# Introduction

The development of new medicines is languishing. Despite the promising potential for research, every year fewer new medicines appear on the market. Developing and introducing new drugs is enormously expensive. To reduce the cost and get medicines onto the market faster, universities, the pharmaceutical industry and the government have to work together more effectively at every stage of the process, from initial fundamental research through to marketing. The Netherlands is also becoming less attractive as a business location for international pharmaceutical companies. A growing proportion of drug development work in the Netherlands is now going elsewhere, to the United States and Asia for instance, where conditions are more favourable. This threatens Dutch research in the long run.

The Academy Committee for Chemistry and the Council for Medical Sciences of the Royal Netherlands Academy of Arts and Sciences organised the symposium 'Cooperation between universities and the pharmaceutical industry. *New opportunities for drug research?*' to debate whether cooperation as it stands at present in the Netherlands is sufficiently geared towards future developments within drug research. All phases of the development process are concerned, but particularly the drug and target discovery phase and the clinical development phase.

The first part of these symposium proceedings comprises summaries of the papers presented. The second part is a recap of the workshop discussions, which primarily explored the current situation in the Netherlands and are therefore in Dutch.



# Summary

Who sets the agenda for drug research in the Netherlands? Is it the government, the patient, universities or the industry? How are these parties responding to the pharmaceutical requirements of specific patient groups, the increasing individualisation of drug treatment and the problem of rare diseases? In order to answer these questions, the Academy Committee for Chemistry and the Council for Medical Sciences of the Royal Netherlands Academy of Arts and Sciences (KNAW) organised the symposium 'Cooperation between universities and the pharmaceutical industry. *New opportunities for drug research?*' on 20 October 2004. The importance of this debate is reinforced by the great changes that have occurred over the past few years in the design and development of medicines. This makes innovation in the pharmaceutical industry a long-term and very costly process. At the same time, society is demanding safer and more effective medicines. Suitable measures are required to ensure that we can continue to meet this demand in future.

The symposium dealt with the options for cooperation and the funding of drug research, but also focused on the barriers. Drug research as a whole must be regarded as a service to the patient. This means not only treating them with new drugs, but also establishing and following the disease process and the outcome of interventions with the aid of biomarkers and diagnostics. The territory covered will become even wider, because people are increasingly designing and testing foods which may contribute to the prevention of disease, known as nutraceuticals (functional foods).

## **Cooperation between industry and universities**

During the symposium, all the parties constantly re-emphasised the fact that drug research requires cooperation. The organisation of innovative research therefore received a relatively large amount of attention during the introductory sessions and workshops. The main topic of discussion revolved around the different ways in which the universities and industry could cooperate. The industry not only includes medium-size and large organisations such as Organon and Solvay Pharmaceuticals, but also smaller-scale and start-up businesses. Outside the pharmaceutical industry, drug research is concentrated on a number of specialist research universities and some non-university institutes. These establishments have joined together with the pharmaceutical industry to form the Netherlands Federation for Innovative Drug Research (FIGON). In the autumn of 2004, FIGON proposed giving this relatively wide area of research in our country the status of key area. A number of other joint ventures for clinical studies have also been set up, such as HOVON (the Dutch haemato-oncology association).

In order to continue to keep pace with innovation in the future, the industry's need for fundamental academic research is greater than ever. This was evident from two lectures about a relatively small pharmaceutical company in the United States and a larger company in the Netherlands. For example, close cooperation between the American company and many universities around the world resulted in the rapid development of the anti-cancer drug Bortezomib. Emphasis was also placed on the need for better predictive *in vitro* and *in vivo* models. These models shorten the path to clinical research on candidate drugs. In turn, fundamental research requires feedback in the form of clinical studies and post-marketing evaluation of new drugs.

According to the participants in the symposium, the cooperation between industry and universities as described above must be given a more clearly defined structure. To achieve this, the partners involved will have to respect each other's sometimes very diverse objectives. Industry representatives believe that this requires companies to be transparent about their internal problems and the progress of their research. Above all, they must be prepared to work together more frequently. Cooperation can also help to reduce their enormous development and marketing costs. At the same time, university groups must make clearer choices, especially as regards their excellent research. To do so, they can use the recommendations of international peer review committees.

### **Clinical drug research**

Clinical drug research in the Netherlands is well regarded internationally and is therefore in principle attractive to the pharmaceutical industry. The industry and university centres generally work well together in developing and testing drugs. However, linking the data files of hospitals with those of general practitioners and pharmacists can use the existing infrastructure even more efficiently. Drug research will increasingly focus on biotechnology products (therapeutic proteins and DNA or RNA products). This places specific demands on clinical researchers. In order to meet these demands, all medical and pharmaceutical training courses must focus greater attention on biotechnology, molecular biology and the general process of developing drugs.

Cooperation between universities and industry is only possible if academic accountability is preserved and if researchers can publish data from the joint research, unhindered. When clinical researchers, in cooperation with industry, wish to evaluate new substances, this can only be done under conditions in which their independence is guaranteed. Companies and university medical centres should set out these conditions, within the existing regulations, in contractual form.

The current regulations governing clinical drug research, both at national and at European level, are considered by all parties to be unnecessarily complicated. They make it even more difficult and costly to conduct these studies. The participants in the symposium therefore predicted a decrease in clinical drug research in the Netherlands. In addition, Dutch researchers are acting less frequently as coordinators of international studies. The complicated regulations are partly a result of their over-in-

terpretation by authorities and industry. Self-regulation is said to be taking the place of external regulation. If researchers take up an active position, draw up their own internal guidelines and set up a detailed project monitoring system within the research institutes, the government will not have to supervise them so closely. To achieve this, it is essential to have a local professional infrastructure in place. At the same time, what the industry requires from the Dutch government is clarity surrounding the regulations concerning translational clinical research. In one of the workshops it was stressed that the patient associations can contribute to the speedy progress of innovative drug research.

### **Protecting knowledge**

The pharmaceutical industry will only take university groups seriously, if they protect their knowledge better and more systematically by adopting a more active policy towards patenting. Not all universities have sufficient facilities to protect knowledge. Moreover, it is also possible to make the move towards a start-up business too soon. Many new ideas first have to be matured through internal incubation. These small-scale incubation projects can only be achieved with additional government funding. However, costly patent portfolios should not be allowed to stifle innovation at the universities. They should be able to find an industrial partner or another means of continuing their projects for patenting purposes within two years.

### **Role of the government**

The symposium participants were of the opinion that, in general, the Dutch government provides too little support for drug research. A long-term strategy, linked to a clear plan, is highly desirable if the sector is to develop properly. Nowadays, pharmaceutical companies are increasingly more searching for settlement abroad. In addition, the funding of university research, which is still of a high quality, has reached an unacceptable level. The symposium participants were afraid that government money would come under even greater pressure. However, new hopeful initiatives are in progress. The Ministry of Economic Affairs has set up a number of projects focusing on innovation (WBSO – a tax scheme designed to stimulate research and development – and Technostarter). In addition, the Ministry of Health, Welfare and Sport has ensured that Europe will be giving priority to drugs that benefit specific patient groups and developing countries ('Priority medicines for the citizens of Europe and the world'). In addition, the five ministries (Economic Affairs; Health, Welfare and Sport; Agriculture, Nature and Food Quality; Housing, Spatial Planning and the Environment; and Education, Culture and Science) have recently cooperated effectively to simplify legislation and regulations, including those relating to drug research.

The strengths of the Dutch research community are the generation of original ideas, which constitute the first steps in the development of medicines, and a good environment that the Netherlands offers for effective clinical drug research. In order to eventually achieve the necessary streamlining of the entire chain from fundamental research to clinical trials, it is high time for a decisive and integrated approach to

drug research in the Netherlands. This requires the further strengthening of fundamental, preclinical and clinical drug research at the universities. It is also important that the exchange of knowledge between academic institutions and industry be intensified.

# Recommendations

## Cooperation

- The excellent research conducted in the Netherlands delivers too few products. One solution to this knowledge paradox is improved cooperation between universities, medical centres, industry and government.
- Being focused is a necessary prerequisite for improved cooperation. The knowledge institutions must identify disease processes and technologies for which and with which research into new medicines will be carried out. The means identified for strengthening the desired cooperation are technology exchange and possible PhD projects.
- Cooperation between academic centres and industry must not only manifest itself at national and regional level but also, more importantly, at European level. This involves smoothing the path from fundamental research via applied research to product development, and vice versa.

## Regulations

- The process of developing drugs, particularly Phase III trials, must be substantially shortened. This can be achieved by:
  - reducing bureaucracy and preventing the over-interpretation of regulations in the conduct of clinical studies. This could reduce the staff/patient ratio during these studies.
  - developing innovative early end points by, for example, using new biomarkers.
- Making it attractive for private individuals, from a tax point of view, to invest in drug and other research.

## Organisation

- Universities, industry and the government must give their cooperation a specific form. The Top Institute Pharma, as initiated by FIGON and shortly to be established, will make a substantial contribution to this.
- Dutch academic groups and industry, must have more input into European initiatives such as ‘New Safe Medicines Faster’, ‘Innovative Medicines’ (candidate European Technology Platform) and ‘Priority Medicines’ (via the European Research Area, ERA-NET). FIGON and European organisations such as the European Federation of Pharmaceutical Sciences (EUFEPS) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) also have a part to play in this.
- The government should facilitate the infrastructure for clinical studies by supporting a network of clinical researchers/research groups. On the other hand, hospitals participating in clinical trials must provide a professional local infrastructure.

### **Cultural transition**

- The image of drug research must be improved. The parties must make it clear that the use of medicines is not, by definition, entirely risk-free. In addition, the importance of the continuous development of new drugs must be stressed. Both the government and the public must accept their responsibilities.
- Improvements can be made in the training of doctors and pharmacists. One possibility is to have specialisation within the courses on the following points:
  - molecular pathology
  - biotechnology/molecular biology and the results for the development of drugs
  - the general process of developing a drug and the relevant regulations. In addition, entrepreneurship must be given greater emphasis within the training courses
- Universities, the government and industry must establish a joint educational programme to improve the way various aspects of the development of drugs are integrated into the training courses. An additional benefit of this is improved co-operation and information exchange between these parties.

### **Knowledge protection/Entrepreneurship**

- The way intellectual property is protected at academic centres must be substantially improved. This is important for knowledge-based business. It is, however, not the intention of universities to take on the business aspects themselves.
- To formalise this, a national standard contract should be drawn up to cover co-operation between universities and industry. This contract would regulate matters such as intellectual property rights, the distribution of rights and proceeds and the policy surrounding the publishing and confidentiality of inventions and discoveries.



## Academic research in the pharmaceutical sciences: the pre-clinical phase

Academic research in the pharmaceutical sciences is focused on the generation of new insights and methodologies for the better and faster discovery, development and use of new, safe and efficacious drugs. The creation of a new drug is a long, complex process with many different disciplines driving the synthesis and selection of the successful candidate. This is a sequence of steps, often referred to as the 'drug-pipeline'. One step drives the next step until a new drug is launched. The pipeline starts with the finding and validation of drug targets. A compound screening process and identification of a lead compound follows this step. Further work in animals and other biosystems (e.g. cell lines, tissue cultures) will give an initial idea of the safety and efficacy profile. It is in the final stage of the pre-clinical phase that the pharmacokinetic behaviour and the drug delivery issues are addressed. In reality, this pipeline contains all kinds of feedback-loops. Findings are turned over from one step, e.g. lead optimisation, to the next step, drug formulation/biopharmacy. Here the new compounds are evaluated and the results are fed back if problems arise.

### Research drivers

The drivers behind drug research are, on the one hand, new basic findings, the scientific drivers. The sequencing of the human genome and the emerging concept of functional genomics pushed the field as new, so far unknown, target molecules involved in generating pathological events were identified. On the other hand, there are societal drivers to search for new drug molecules. The search for new antibiotics to fight resistant bacteria is high on the priority list. The same is true for safe and more effective vaccines. Recently, the fear of bioterrorism and the need for protective measures has prompted research in this area. A further trend is that the economics of the pharmaceutical market place increasingly set the agenda for the industry, thereby also indirectly influencing academic pharmaceutical research.

### Research institutes

Academic groups have traditionally worked on one aspect of the drug discovery or development process. Pharmacology or pharmaceutical technology departments in academic centres defined their own research goals and worked in 'splendid isolation'. They were small. Nevertheless, this has led to important new findings and an understanding of basic mechanisms. The idea of following the industrial 'pipeline' ap-

proach for creating new drugs was neither appreciated nor followed. Nowadays, one can observe trends towards increasing group size in order to reach a critical mass, focusing research on particular subjects and structuring academic drug research institutes more along the lines of industrial operation: the 'drug pipeline' including the feedback loops. This process is driven, for example, by advice from internal and external review panels. Currently, research institutes concentrating entirely on different aspects of drug research can be found in Leiden/Amsterdam (Leiden Amsterdam Centre for Drug Research), Groningen (Groningen University Institute for Drug Exploration) and Utrecht (Utrecht Institute for Pharmaceutical Sciences).

## **UIPS**

The mission of the Utrecht Institute for Pharmaceutical Sciences (UIPS) is to perform conceptual research (UIPS produces concepts, not products) focused on the development and application of medicines; to train PhD students in order to provide society with a variety of learned pharmaceutical researchers; and to focus on peptides, proteins and gene research. The six pillars of UIPS are: the disease itself, targets (immunopharmacology and psychopharmacology), lead compounds, delivery systems, drug use and the drug itself. Despite the fact that this looks like a sequence it is actually a circular system where all the different steps interact with each other. This system is particularly suitable for an institute like UIPS, because the people working on the different parts of the circle know each other and interact closely.

Other institutes like the Cardiovascular Research Institute Maastricht (CARIM) and the Rudolf Magnus Institute (RMI) focus on special parts (e.g. cardiovascular, central nervous system) of the drug finding and assessment process. These institutes have made clear choices regarding their research objectives. By doing so, the limited 'first flow of money' budgets for research has allowed them to fund less, but larger-scale and more focused research of supercritical size. This creates an excellent starting position from which to bring in money from competitive sources. Focusing has long-term consequences. The Netherlands, being a small country, may not be able to sustain all the academic disciplines related to drug research. The presence of academic groups working in pharmacognosy, for instance, has been reduced to a minimum in the last decade. As the current master programmes will be closely linked to research, educational expertise in non-selected research areas will disappear. That is the consequence of choosing to work with a limited number of focused research groups who can compete with top groups at global level. At present, decisions for focussing are made independently in the different universities. Preferably, this process of selecting research fields in the pharmaceutical sciences should be coordinated at national or even international level and all the consequences (including political) should be considered. Quality assessment should play an important role in this selection.

## **Academic research in the pharmaceutical sciences**

### *Trends...*

- Focusing
- Group size increases/critical mass
- Centralized ‘orchestration’
- Quality assessment

### **Reaching out**

In the Netherlands, drug research-oriented institutions communicate through the Netherlands Federation of Innovative Drug Research (FIGON). FIGON offers a platform for discussion and action in advanced pharmaceutical research in the Netherlands. Another way for the academic world to reach out (from ‘concept to product’) is to encourage the formation of spin-off companies based on academic findings and/or expertise. Programmes such as those run by Biopartner/STIGON have been highly successful in guiding these spin-off companies through their start-up phase. Unfortunately, the new plans of the Dutch Ministry of Economic Affairs do not seem to include direct financial incentives for academic spin-offs.

### **Interactions between universities and industry**

Universities are interested in concepts, industry is interested in products. Collaboration between the two parties is not new. Successful collaborations between individual academic scientists and pharmaceutical companies and between academic groups and industry as a strategic alliance have now been in existence for a considerable time. The Unyphar-project, as an example of such an alliance, is a successful collaboration between Yamanouchi, Utrecht University, the University of Groningen and the University of Leiden, orchestrating a laboratory without walls. Research done as part of this collaboration was published by the academic partners and resulted in patents for Yamanouchi.

Despite the willingness of the universities to spin off their expertise and the encouragement of this by the Dutch government’s Innovation Platform, the Netherlands is facing a knowledge paradox: academic research groups do an excellent job, but the activities, business and products resulting from this are limited. Over the last two decades ideas about how pharmaceutical research should be organised within universities have changed. Focused research groups have been formed. These groups compete successfully with top international groups. FIGON will make an attempt to set up a Top Institute Pharma and try to recruit Dutch pharmaceutical research groups with a quality label to join the institute. Further attuning of research directions and stimulation of academic drug research through a platform such as FIGON, both at the national and international level is required.



## Oncology drug discovery: cooperation between academic institutions and industry

Basic research has traditionally been conducted at academic institutions. Historically, large pharmaceutical companies with technologies in combinatorial chemistry and pharmacology acquired basic research from academia and continued research with the intention of developing a new drug. Recently there has been an enormous increase in the number of small biotechnology companies that acquire some of the early work from the academic research centres. Of the 2500 biotechnology companies worldwide, however, only a handful have developed any products from these activities. Still, many of them will eventually turn their discoveries over to large pharmaceutical companies for further development.

Industry is expanding its basic research. Millennium Pharmaceuticals (MP), a relatively small American company employing 1500 people, is a biotechnology company that has a significant proportion of its employees doing unrestricted basic research. On the other hand, many universities have recently started creating drug discovery units, which not only perform basic biology research, but also discover targets, find the drug and then move it on to pharmaceutical companies. The wall between industry and academia appears to be slowly disappearing and hopefully we have entered a transitional phase in which both parties will appear to create better drugs for patients.

### **The role of biotechnology companies**

Systems biology seems to be the key term for present-day drug development. An enormous array of technologies is now coming on-stream. This makes drug development more complicated, because for many pharmaceutical companies it is almost impossible to build all the necessary technologies in-house. This is where the first critical link between industry and academic institutions begins: to be able to provide the technologies that are required to take a drug through the entire developmental process. Millennium Pharmaceuticals develops in-house model systems and works with academic institutions, which provide a wide range of clinical samples for high-throughput screening and sequencing in order to identify pathways within a disease. Such pathways are then used to identify target molecules, which may lead to the development of novel therapeutics for the underlying disease. This link provides a tremendous interaction between academic institutions and industry. Target identification is now done by means of high throughput screening and transcriptional profiling. Primarily the biotechnology companies currently undertake these techniques, although academic institutions more frequently use fairly large-scale and expensive

facilities (at least in the United States). It is however unlikely that these institutions will make this a major component of their activities due to the high cost of these facilities.

### Collaboration: a case study

The full development of a drug, from the basic science to a new safe and effective therapeutic will take an average of fourteen years (see figure 1). A substantial part of this time is spent on the approval process in both the United States and Europe. The collaboration between MP and different academic institutions and cancer centres recently led to the development of a novel therapeutic, by MP, within a much shorter time than fourteen years. The ubiquitin-proteasome pathway is an example of one of the many biological pathways that were discovered at academic institutions. The proteasome-pathway was identified in the seventies, as an energy-dependent mechanism for protein degradation. Short-lived regulatory proteins that are destined for death are attacked by ubiquitin ligases. These ubiquitinated proteins are then recognized by the 26S proteasome present in all cells. This allows the breakdown for antigen presentation and amino acids. The novel therapeutic developed by MP is a proteasome inhibitor.

### Early collaboration

The first sign of collaboration was in the nineties when MP worked closely with the investigators of the pathway to study the design of an inhibitor for the proteasome. The next step, finding a target, was completed in collaboration with individual scientists who worked on the proteins degraded by the proteasome. This provided MP with the knowledge it needed to make the right decisions about which clinical pathways

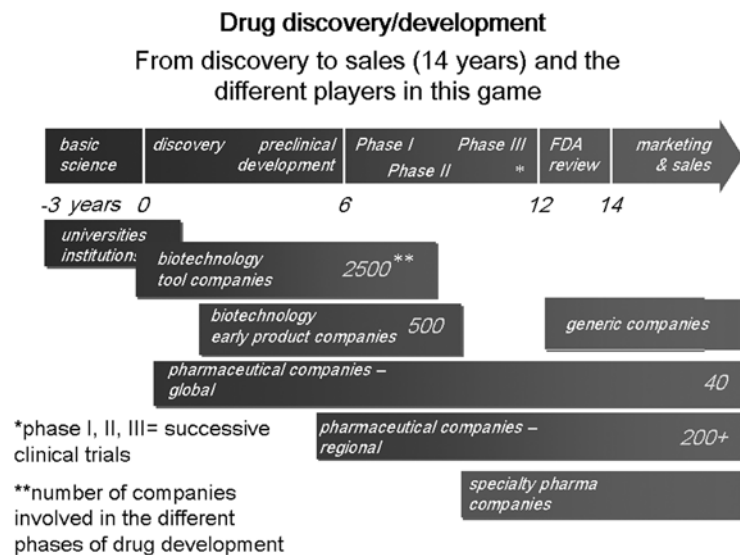


Figure 1

would be used to determine whether these agents would be beneficial for inflammatory diseases or for oncology. With insights gleaned from studies of substrate specificity conducted at academic institutions, MP initiated a rational drug design effort and identified specific reversible inhibitors of the proteasome by 1995. Enhanced understanding of the ways in which these inhibitors bound to the proteasome was obtained when the academic institutions shared the crystal structure of the target. With potent inhibitors in hand, the question arose as to whether they had additional functions other than to proteasome inhibition. The National Cancer Institute ascertained that, at least in vitro, the inhibition of proteasome with this molecule generated a unique signature of inhibiting the growth of cancer cell lines. This new anti-cancer agent was called bortezomib.

The next step in the drug development process was to test Bortezomib in animal models. The early pharmacological tests were performed on mouse lung cancer models at Harvard medical school. Since 1997 MP conducted joint laboratory meetings with a myeloma specialist at the Harvard Medical School to share the basic research on this mechanism. Much of the early in vivo pharmacology research was done jointly by both MP and the academic collaborators, one of them being the University of North Carolina, with whom relationships were formed early in the drug discovery process. Animals were treated with a vehicle, bortezomib alone or in combination with conventional chemotherapeutics to show that the combination could be synergistic. The results from these animal studies provided the rationale for MP to initiate phase I clinical trials in cancer patients.

### **Clinical trials**

The first clinical trial began in 1998, in which a fairly striking activity in multiple myeloma was observed. Phase II clinical trials quickly ensued, performed in collaboration with fourteen myeloma centres in the US. The enrolment for this trial was completed in approximately ten months, one of the quickest accruals for a myeloma trial of this size in the US. At the beginning of this trial it was decided whether tumour-RNA isolated from patients at the time they entered the trial would predict response to a novel therapeutic. This required an enormous collaboration between the fourteen myeloma centres and MP. There was evidence of some early markers that predict responsiveness; these markers are being validated in a much larger setting.

More recently, this novel agent was tested against standard therapy in a randomised phase III clinical trial, as part of a huge worldwide collaboration. This clinical trial was conducted at 93 clinical trial sites across the world with 669 patients enrolled in approximately one year. This trial, whose primary objective was to assess the difference in time to progression, demonstrated that there was a significant improvement in time to progression in favour of the novel agent. Additionally, it also showed a survival advantage in favour of the novel agent. This was the first time a myeloma clinical trial has demonstrated a survival benefit of any therapy other than stem cell transplantation in relapsed multiple myeloma, including second-line multiple myeloma.

MP was able to develop a master agreement template to be used when contracting with the collaborating academic institutions. The template agreement covered both the clinical trials and the basic science stemming from the trials, and defined standard terms for conducting the clinical trials and for the sharing of Intellectual Property-rights. The template agreement was designed to facilitate agreement with the participating sites, making it easier for MP to move quickly into clinical trials by avoiding the typically lengthy negotiations.

### **Approval**

Thanks to this trial, MP was able to rapidly meet the requirements of both the European and the US regulatory agencies. This would have been impossible without worldwide collaboration. In May 2003, approval in the US was achieved for a novel therapeutic to treat multiple myeloma, the first new therapeutic to treat this disease in twenty years. Approval in Europe followed in April 2004. In many of the different stages of the development process, including pathway identification, drug design, pharmacology, tumour selection, mechanism of action, early clinical trials, and even during the approval process, MP collaborated with different academic institutions. These collaborations made it possible to develop this new therapeutic and shows the importance of establishing partnerships at an early stage of drug development, with both academic institutions and other organizations.

### **Future collaborations**

How should the collaboration between academia and industry move forward? There is still much to learn about the proteasome inhibition. Research in this area will be performed in close collaboration between industry and academia. In recent years there has been much greater openness to collaborative discussions about technology transfers between academic institutions, biotechnology companies and large pharmaceutical companies. This has resulted in a flow of scientific expertise, technology and patents from the academia to biotechnology and pharmaceutical companies. What used to take four years between lawyers from these institutions to draw up a contract is now happening in a matter of months.

The research funding for the academic institutions comes from the National Institute of Health and various foundations. This led to criticism about whether it is ethically right that academic research funded by the government should end up as a profit centre for the pharmaceutical industry. This discussion is definitely set to continue.

Traditionally, small biotechnology companies transferred molecules or technology to large pharmaceutical companies. Nowadays, biotechnology companies are capable of handling the entire drug development process on their own. To ensure that valuable collaborations continue between academia, biotechnology companies, and large pharmaceutical companies, it is important that these three parties understand their specific expertise, the relationships among them, and have a free flow of information.



**Partnership: The Five Success-Drivers**

1. A genuine interest in partnership between Science & Technology Institutions and industry with focus on commercialization
2. Incentives and infrastructure to assure transfer of knowledge / technology
3. Critical mass in resources – through public and private funding
4. Flexibility in the educational system
5. Attention to human capital  
...a cultural change is required

There is a bright future for collaboration between the three parties. The imaginary wall between academia and industry, at least from the biotechnology perspective, is starting to erode. As the Bortezomib story illustrates, this allows for a much more open discussion which may eventually lead to new drugs.



# Clinical drug development in oncology

Cancer is currently the second most common cause of death in the western world. It affects one in three people and it is a particular problem of the ageing population. Often, local skin cancers (basaleomas) and some other local diseases are not included in the statistics, while about 60 to 70% of patients will still die from metastatic diseases. Cancer threatens the whole body and as long as prevention and early recognition are inadequate, a systemic treatment is of great importance.

The Netherlands is an ideal feeding ground for performing clinical trials, particularly in oncology. An immediate problem in clinical trials in oncology is the absence of an appropriate short-term outcome, as in trials in hypertension, diabetes and hypercholesterolemia. The aim of clinical trials in oncology research is to improve survival or time to progression, which is a relatively long-term outcome and one of the reasons that trials in this field of research can take a long time. Something else that is peculiar to oncology is that it treats a disease that is fatal to patients in the short term. Because of this, slightly more side effects from new therapeutics tend to be accepted than one would expect to accept with any other disease.

## Looking at both sides

Looking at oncology research at universities and the pharmaceutical industry both parties have their strengths and their weaknesses as one can see in figure 1:

The mutual strengths and weaknesses in oncology	
<p><b>PHARMA STRENGTHS</b></p> <ul style="list-style-type: none"> <li>- Good basic research for drug discovery</li> <li>- Resources available</li> <li>- Good knowledge of regulations</li> </ul>	<p><b>ACADEMIA WEAKNESSES</b></p> <ul style="list-style-type: none"> <li>- No basic research aiming at drug discovery</li> <li>- Decreasing access to resources</li> <li>- Limited knowledge of regulations</li> <li>- Very poor IT support</li> </ul>
<p><b>PHARMA WEAKNESSES</b></p> <ul style="list-style-type: none"> <li>- Limited clinical awareness</li> <li>- Need to create networks repeatedly</li> <li>- No awareness of local IRB limitations and demands</li> <li>- Unrealistic demand in accrual time</li> <li>- Bureaucracy</li> </ul>	<p><b>ACADEMIA STRENGTHS</b></p> <ul style="list-style-type: none"> <li>- High level clinical investigators</li> <li>- Easy access to existing networks</li> <li>- Awareness of local IRB limitations and demands</li> <li>- Realistic estimation of accrual time</li> <li>- Bureaucracy</li> </ul>

Figure 1

## **Regulations**

It is inevitable that the protocols for performing clinical trials will have to be reviewed. It is difficult to follow the preclinical information and it is increasingly difficult to follow the clinical information. A survey among members of Institutional Review Boards (IRB) revealed that the self-declared level of competence on a variety of issues in phase-II clinical trials was low. It appears that doctors have a major difficulty in understanding the trial and that there are too few people available in any of the countries that have the detailed knowledge needed to assess the protocol properly. The people involved should be provided with more regular summarised information on general principles of cancer treatments and protocol introduction should be made simple, complete and unambiguous.

Furthermore, directives issued by the European Union will have most effect on academic trials. This will create a potential for the pharmaceutical industry and it is important that universities are aware of this and make themselves familiar with these regulations. The Dutch government has been supportive in this by publishing a manual to help clinical investigators cope with the rules and regulations of the European clinical trials directive.

## **The importance of a network**

During the development of a drug, the wrong decisions can be made and one could easily kill off a newly developed drug. It is then difficult to recover the development process and bring it to a successful conclusion. This is one of the fields for which the pharmaceutical industry is not always suitably equipped and is consequently one of the reasons for the long period between this stage of clinical studies and drug registration. When the expected time of a trial is compared with the actual time of trials in universities and trials in the pharmaceutical industry, industry does need much more time to complete a trial. This shows the advantage of a properly functioning network. The selection of centres for the trial is easier and more successful when a network exists. Without this network completion of the trial is delayed, with the unavoidable consequence of financial loss.

The number of Dutch accruals in the European Organisation for Research and Treatment of Cancer (EORTC) is decreasing. This is due to a shift from phase III and IV trials to phase I and II trials. Actually, more studies are performed, but with fewer patients per study and fewer patients in total. In spite of this decrease, the Netherlands is still top of the list of accruals in a big, Europe-wide EORTC network. So the Netherlands has a fantastic accrual in network trials, from which many are also performed in collaboration with the pharmaceutical industry. However, when looking at the estimated accrual by funding resources in oncology clinical trials in the Netherlands, it is the pharmaceutical industry that comes top of the list. Collaboration seems to be a good option for both parties to complement each other.

## Administration

With increasing regulation, the number of support staff required for performing trials is increasing. Since the Good Clinical Practice (GCP) guidelines and the Dutch Law on Medical Scientific Research (WMO) were introduced, the number of support staff in performing clinical trials has increased twelve-fold (see Fig. 2). The reason for this increase in support staff is partly related to the increase in regulation, but mainly related to the interpretation of these regulations by industry: pharmaceutical companies are over-protecting themselves from substantial losses: the bureaucracy of pharmaceutical companies, with the consequent enormous rise in drug development costs. It is of course important to realise that the risk in drug development is biggest in phase three clinical trials: the risk of making the wrong decision and suffering a huge financial loss. To solve these administrative problems, regulation should be decreased, the procedures and forms involved should be simplified and standardised, submissions can be digitalised and the level of professionalism in IRB support staff can be increased.

## Decreasing staff numbers

The decline in the number of physician scientists, a decline of more than 35% in fifteen years, is problematic. The number of clinical trials being performed is increasing, which is partly due to the fact that a phenomenal molecular knowledge is available nowadays and partly due to the increase in regulation; the GCP directive, for instance, forces clinical investigators to do more trials than were required before this directive came into effect. This increased number of clinical trials has to be performed by a declining number of physician scientists. In the United States the market for clinical investigations is saturated. Despite having targets identified and drugs created it is impossible to test them, because of this lack of clinical investigators. Although the Netherlands is not yet facing this problem, and there has been no decrease in clinical trial protocols submitted over the last four years, the general

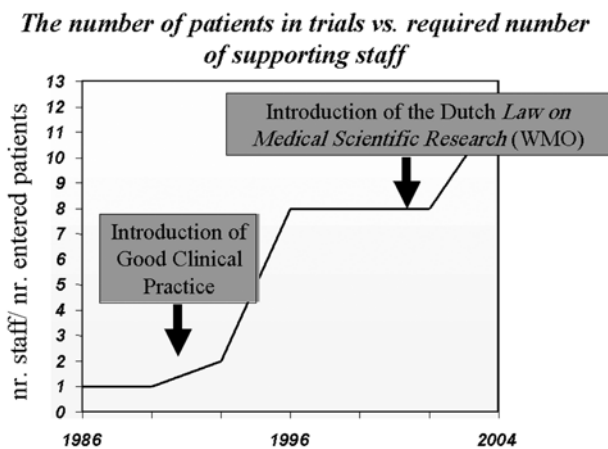


Figure 2

feeling among Dutch scientists is that a shortage of young scientists is imminent. It is therefore necessary to train medical students to become good doctors with an awareness of the need to perform good drug research and then train them to become highly professional clinical investigators. Oncology workshops have been developed on clinical trials methodology to inspire young doctors to become clinical investigators and to teach them to conduct these studies in a proper manner.

### **Image problem**

Drug development research has an image problem, which is mainly fuelled by the government and the media. Too often the image is created of the clinical researcher and the pharmaceutical industry using the unfortunate patient as their guinea pig, although this is not the perception of many patients. Furthermore, the roles of those involved in clinical drug research and their mutual relationships should be improved. Besides this, transparency should be improved in terms of study performance and the funding involved.

The current Dutch situation is not bad: the average time to protocol approval is still, despite the many problems, about three to five months. The Netherlands is still an ideal country in which to perform oncology clinical trials, despite all the regulations, and has an ideal climate for securing the closest possible collaboration between industry and universities. This collaboration is necessary if we are ever to achieve our aim. Both parties have to consider each other as partners, not as tools and each should speak the other's language. Cooperation between universities and the pharmaceutical industry can solve existing problems more easily than either party on its own. They can and will have to work towards an equal scientific partnership to ensure the rapid development of new active agents.

## Drug research from an academic perspective

Until a decade ago the drug development focused mainly on small drugs. The clinical development strategy for small drugs is obviously very different than it is for the biotechnological drugs that are developed today, not to mention the difference with stem cell transplantation with genetically modified stem cells or gene-therapy. Most of the small molecules have been developed by high-throughput screening using cell systems, followed by testing on animal models, phase I to III trials and finally the registration trials. When looking at this model, universities became progressively less important in the last forty to fifty years.

Very early in the developmental process of biotechnological drugs (meaning antibodies, antisense oligonucleotides, gene therapy, cell therapy) extensive knowledge of the disease and of specialized animal models is needed. These kinds of models are not rapidly available and take a long time to set up. A biotechnological company would need about a year to set up such a specialized model. Very early in the drug development process also access to patients is needed. And for some of the drugs specialized (pre)clinical facilities are necessary (e.g. gene therapy production facilities). Specialized animal models, patients and special facilities are often not present in the industry itself. This shows that the classical business model for the pharmaceutical industry, which implied the development of all necessary components in-house or maybe in collaboration with one academic partner, has changed dramatically. The main contact between pharmaceutical industry and universities was through subsidiaries and sales (see figure 1). At present, biotechnological companies approach clinical researches already in the beginning of the drug development process to start the development of an antibody or gene therapy. On the other hand clinical researchers even approach biotechnological companies quite often with an idea for further development. This requires a frequent interaction between universities and biotechnological companies during research, development and regulatory phases of the development process (see figure 2).

### Collaboration

Collaboration between pharmaceutical industry and universities in the Netherlands is far from optimal. Whereas strong (pre-) clinical research groups do exist, their ability to employ their expertise to make drugs has been weak. The Dutch (pre-) clinical research groups have problems with the protection of their intellectual property and very few academic spin-offs exist in the Netherlands. Compared to other European countries it is remarkable how little is invested in drug research in the Netherlands.

## Classical business model

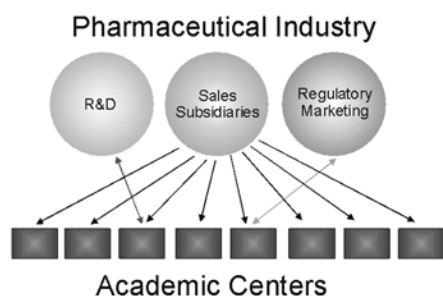


Figure 1

## New business model

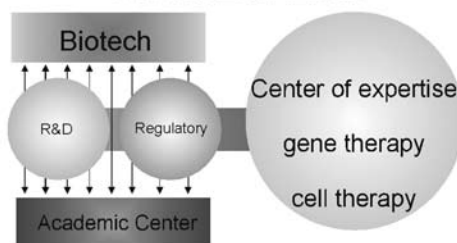


Figure 2

To facilitate this collaboration infrastructure should be set up, like centres of expertise and special facilities.

### A case study

In 1985 TNF-antibodies were discovered and it was found out that these antibodies were effective in Baboon sepsis. Subsequently was found that the Tumour Necrosis Factor (TNF) was expressed in many inflammatory diseases. This led to research of TNF antibodies in rheumatoid arthritis and in Crohn's disease in 1992. Patients with Crohn's disease who were refractory to all other therapies showed a complete remission of their symptoms after two weeks of treatment with these TNF antibodies. The TNF was expressed on the membrane of T-lymphocytes in the mucosa and worked mainly by bringing these cells in apoptosis. The idea was originally that the TNF was blocked, but it appeared that a T-lymphocytes-killing compound was targeted. This was a remarkable result, because T-lymphocytes are driving this disease. The important result of this study was that in Crohn's disease some of the anti-TNF binds very well, and some of the antibodies did not bind to T-lymphocytes. Because there were and still are many biotechnological companies making anti-TNF, the results of this study should be brought convincingly. Therefore a mouse model was developed in which apoptosis induction in the colon of the mouse was shown *in vivo*. Later on apoptosis induction on T-lymphocytes was also shown in human beings. This case study is an example of research for which the pharmaceutical industry had the main research material, the antibody, but starting a trial was an academic initiative and most of the research was done in universities.

### Human resources

During this process many phases are passed through. First the TNF was discovered followed by pre-clinical studies to get a proof of concept, phase I to III trials, proving that the mechanism of action was different than anticipated (which happens very frequently in drug development), exploration of other indications, registration and the finding that some anti-TNF fail. For all these different parts of the research



process people are required that have knowledge of (modern) molecular and cell biology, knowledge of (bio) technology, knowledge of drug development, including regulatory issues and knowledge of human diseases. Of these requirements Dutch doctors meet only the last one, their knowledge of human diseases is good. This leaves the Dutch universities with a staff problem. To solve this problem training of doctors should in the future also encompass biotechnological knowledge and knowledge of drug development and accompanying regulations.

## Conclusions

Many problems have to be solved in the Dutch drug development. Next to the mentioned lack of qualified people, lack of innovative start-ups from universities, lack of clinical biotechnical research structure in most Dutch academic centres and a slow introduction (reimbursement) of biologicals, also a lack of funds and a lack of a drive for innovation in Dutch healthcare exist. Current regulation is not able to cope with new developments. To solve these problems the training of clinicians should be improved: more emphasis should be laid on molecular pathology, biotechnology and on drug development/ regulation. This will stimulate innovation in drug research. For rare diseases or diseases that require specialized treatment, expert (clinical) centres should be set up. The Netherlands needs (a) centre(s) for Good Manufacturing Practice (GMP)-production of biotechnological drugs (antibodies, vectors, cell therapies). A more professional approach towards protection of intellectual property by academic medical centres is important just as is a more professional approach towards seed capital funding for biotechnological companies. Furthermore the Netherlands should enhance its representation in the European Medicines Agency (EMA), the main drug regulation and registration agency in Europe. Decisions of the EMA do apply to the Netherlands but unlike many other European countries, we lack a strong representation in this organisation. Only when these improvements will be executed the Netherlands will be able to keep up in global drug development.

### What can be done?

- Improve training of clinicians:
  - more emphasis on molecular pathology (doctors need to be able to handle a pipette)
  - more emphasis on biotechnology
  - more emphasis on drug development/regulation
- Expert (clinical) centers for diseases that are rare or require specialized treatment
- Netherlands needs (a) center(s) for GMP production of biotech drugs (antibodies, vectors, cell therapies)
- A more professional approach towards protection of IP by academic medical centers
- A more professional approach towards biotech seed capital funding



## Universities and industry: a new future together?

Traditionally, the pharmaceutical industry has been based on discovery constraint. The available technologies made it possible to screen many compounds for usefulness, but it was difficult to find targets and to identify the right molecules. The limiting factor has slowly moved towards the present-day development constraint. For instance, finding patients is increasingly difficult and many pharmaceutical companies are therefore switching to other countries. Furthermore, instead of the usual blockbusters, the pharmaceutical industry will have to change its strategy to develop products that are more tailored to patients and diagnostics should be combined more closely with therapeutics.

Besides these changes in the development of drugs, changes can also be seen in the financial aspect of drug development. In the past long product life cycles were the rule, but today they are increasingly the exception. Because of intense price competition when a new product is introduced on the market, one can expect a therapeutic substitute within one year. The extensive availability of knowledge and widely diffused technologies make this possible. This leads to a paradox in pharmaceutical research and development: there has never before been so much technology, so much information on the biology and mechanisms, so much money spent on research and development and yet output has not been this low before. This can partly be explained by the fact that drug development is becoming increasingly difficult, because of its gradual nature: the 'easy' things have already been done.

### **Changes in the economic landscape of drug development**

The challenge for pharmaceutical companies is to maintain productivity in an environment that is increasingly complex in its scientific, medical and regulatory aspects. Fortunately, there is a willingness to pay more for medicines, provided that the products are innovative and have been developed with an improved benefit-risk ratio and a sound pharmaco-economic profile. The income statements of the top twenty of pharmaceutical companies in the world show that in comparison with other industries the pharmaceutical industry makes too much profit. This is probably one of the primary problems of the sector: with so much profit there is no need for any effort to enhance it. Unfortunately, or fortunately, as the case may be, this is not going to last much longer. Calls for price reductions and restricted access to treatment are increasing. These factors have an important effect on the total financial situation: with a 25% reduction in the sales price of a product, the company will have less profit.

Nevertheless, the research and development costs for the drug, the cost of selling the product and the cost of goods will remain the same. Some internal rearrangements of expenditure will be possible in the company, e.g. spending more on product research and development than on marketing and sales. But in the end less income means less financial resources for product development. This will have its effect on the discovery and the clinical aspect of drug development and in the end the problem will expand to the universities and the patient. And, after all, it is the patient we are working for!

### **Opportunities to change the paradigm**

Deciding at an early stage what is worth developing into a useful treatment and what is not should lower development costs. There are a couple of areas in which promising progress can be made. Instead of the traditional inefficient drug design by means of trial and error, drug design should be rationalised and new techniques should be used, e.g. conducting research *in silico*. Instead of the common erratic clinical endpoints, clinical endpoints should be developed as part of the discovery. Instead of the usual large numbers of patients in clinical trials, which causes a dilution in phase III to fail, the formulation of better clinical endpoints can lead to fewer patients and fewer studies. Instead of having the same paradigm for different products, the organisation and processes should be adapted to meet specific situations. Finally, instead of the usual focus on the delivery of the product, the focus should be on disease management, a combination of diagnosis, treatment and follow-up. In conclusion, the question should be ‘how do we match the drug to the patient?’ instead of ‘how do we match the patient to the drug?’.

### **Where can improvements be made by the pharmaceutical industry?**

New technologies are under-utilised in clinical development and new diagnostic techniques are not developed at an early stage, when they should be. An example of this are biomarkers, which can be used as measuring devices for the diagnosis and monitoring of patients. But biomarkers will only work if they are included in early discovery programmes. To be useful, they have to be developed together with the early compounds. If this is done properly, it may be possible to convince regulatory agencies of the fact that these biomarkers can be used as surrogate markers and speed up the process by coming earlier to a decision on whether the compound / mechanism tested may do something or is completely worthless. The present paradigm of phase I-II-III trials has to be replaced by a new development paradigm. This is only possible when different methods of measuring are available.

The blockbuster versus patient-tailored products forms a dilemma in drug development. Patient-tailored products are often smaller products and will be no problem for small pharmaceutical companies. But big pharmaceutical companies cannot afford smaller products, and have to make their profit with blockbusters.

Besides the major contribution made by pharmaceuticals in general to increase our life expectancy, pharmaceutical products are now also contributing to a greater ability

to function, to a higher quality of life. Public opinion often forgets that contribution. After all, productivity is measured predominantly in financial terms, not by contributions to health. The industry should also be less arrogant and have an open mind. The arrogance of many pharmaceutical companies has, together with lower productivity, contributed to the bad image of pharmaceutical industry. This shows the need to improve the image of the pharmaceutical world.

### **Where can improvements be made by universities?**

Some fifteen years ago, a good publication in a high-level scientific journal used to be the start of a small company. Experience has shown that it is not that easy any more. The intellectual property rights that gave rise to such a start-up company should in future stay in the parent institution. It is of great importance that intellectual property becomes a focus in the process of drug development, together with the experience of the employees. Universities cover both the educational and the research aspects, which make them the ideal place for this focus.

The education system needs to be adapted to the current multidisciplinary approach in drug development. Many new people are not trained in a multidisciplinary way, but focus on one area. Teaching them to focus on multiple areas can increase these people's productivity.

### **Collaboration**

Dutch academic research, fundamental, preclinical and clinical, and the Dutch education system are of a high quality. There is a small-scale but high-quality pharmaceutical industry. Its success was evident last year when it discovered compounds, which were successfully sold to big American companies. The Dutch universities and the Dutch pharmaceutical industry could together build a firm foundation for a healthy drug developmental area, which could easily compete with other important regions in the world. Unfortunately, they often fail to bring all their good qualities together and realise their potential. It is important for the Netherlands to realise that research and development should be geared to the global market, otherwise there will be no return on investment. However, there is no need for Dutch companies and Dutch research groups to go abroad; good science is practised everywhere in the world. Only the right processes have to be found. And as long as the existence of upcoming developing countries like India and China is not ignored, they will not constitute a threat.

### **What improvements can be made?**

- Universities, regulators and industry should define jointly educational programmes for the future. Improved systems for internships have to be implemented to exchange people between these three key players. Part of this should be the increased involvement of industrial experts in the educational system.
- A number of high-value-adding focus areas for the future has to be defined, e.g. target identification and validation, biomarkers and clinical proof-of-principle.

- Strategies and approaches should be defined to keep the intellectual property in the Netherlands, because that is the key asset of a country. In some countries project management groups have been established to provide universities with project management to assist with the development of academic inventions up to proof-of-principle. The researcher/research group will be able to sell it to big pharmaceutical companies and earn not 5 million, but 100 million dollars while keeping the employment and the network around it. These project management groups are comparable to the ones in private companies but are funded by the government.
- Government grants should be provided.
- A framework should be set up to give concrete form to all of the above-mentioned measures. If these measures are not taken many opportunities will be lost. An institute for drug discovery or drug research would be one way of arriving at a collective initiative. This institute should not be too nationalistic and should only take on research not already undertaken by other groups/countries.

In collaboration with the regulatory agencies, ways should be found of working together more closely as partners, rather than having the present adversarial relationship. The whole pharmaceutical sector, private and public, has an ethical problem with the enormously long period before the invention of a new drug reaches the patient, which will often take fifteen years. With all the highly qualified people in the Netherlands, clinical researchers and regulatory people, it should be possible to make the drug development process much faster.

#### EDUCATION

- Joint programmes by academia, industry and government.

#### RESEARCH

- Define a number of high-value-adding focus areas for the future:
  - target identification and validation
  - biomarkers
  - clinical proof-of-principle
- Create a framework for continuous interactions between industry and academia.
- Globalisation of pharmaceutical research is a given and a must.
- Protect intellectual property.

#### Conclusions

First of all, globalisation of pharmaceutical research is a given and a must. Second, the expertise should be left in its efficient environment and people should work in suitable networks. In other words, do not lure all the good researchers away from their academic institution, as pharmaceutical companies often do, but motivate them to form a network with you.

The Netherlands can make a significant contribution, provided that it finds better ways of increasing its potential. And it better do so quickly, before it is too late.

# Entrepreneurship at universities

## Introduction

The subject *Cooperation between universities and the pharmaceutical industry* fits in well with the Dutch government's innovation policy and appeals to the Ministry of Economic Affairs. This requires entrepreneurship on the part of the universities that is aimed at increasing the innovation potential of the Netherlands. Cooperation between research driven life science businesses and educational institutions is of the greatest importance and has been everyday practice for years. The ministry is aware of the importance of interaction between life science businesses and educational institutions and will contribute to this in different ways.

## The Innovation Policy

To stimulate innovation in the Netherlands an Innovation Policy was published in autumn 2003 in the so-called Letter of Innovation from the minister and secretary of state of Economic Affairs. This policy is composed of two main pillars. The first is to create more innovative businesses. A more innovative climate should in general lead to more innovative businesses. There are three ways to achieve this:

- By starting up new innovative businesses, 'technostarters'. It was for this purpose that Biopartner was set up in the life sciences. From 2005 onwards, the intention is that the generic Technopartner Program will fulfil this role for the coming years.
- By having existing small and medium-sized enterprises carry out more innovative research; for example, an accessible system has been set up for this purpose, enabling businesses to use vouchers to benefit from a short consultation provided by an educational or scientific institution.
- By stimulating foreign innovative businesses to set up operations in the Netherlands. This is the work of our National Foreign Investment Agency as well as the regional agencies.

The second pillar of the Innovation Policy is to increase the focus upon and critical mass in areas of strategically important innovation. The Netherlands is small and research is precious. Therefore, choices must be made in order to ensure that our efforts are not unnecessarily diluted. The Letter of Innovation sets out what are known as principle innovative points, on which the focus of the research must be directed. The government does not select these areas itself, they emerge as a result of market forces. This involves those innovative areas in which the Netherlands is strong, both with regard to knowledge as well as business activity. These are the areas that have

the greatest potential to contribute substantially to sustained economic growth.

Examples of this Innovation Policy that have been in operation for some time are the so-called Technological Top Institutes (TTIs). The Wageningen Centre for Food Sciences is an example of a TTI. The purpose of these initiatives is to create long-term economic value (valorisation) in the form of innovative products or production processes. They involve close cooperation and commitment from the academic world and the industry.

### **What does this innovation policy mean for life sciences?**

The number of start-up companies has increased by a factor of three in the last five years when compared to the nineties. About 60% of our dedicated life sciences companies were established during the last four years. This indicates a culture shift or, even better, an increase in entrepreneurship within science and educational institutions. The Biopartner Program has certainly made a significant contribution to this. A final evaluation will be presented in the beginning of 2005. Looking at the subsidies consumed can monitor the field of life sciences. Life science businesses are making intensive use of the technological cooperation schemes (the so called IS and TS scheme); tenders held in 2004 take up more than 30% of the total budget; the 'red' biotechnology takes about 1/3 of these subsidies for life sciences. We have used the lessons learned from this five-year Biopartner program for the setting up of Technopartner. This is a programme that will structurally promote development of new technostarters and will do this in all fields of technology, including life sciences, from 2005 onwards.

### **Life sciences action plan**

The government stated at the beginning of 2004 in the Life Sciences Action Plan how the General Innovation Policy is put into practice in the field of life sciences. In this case, life sciences encompasses much more than medicines and human health. It also deals with food and food production, fine chemistry and sustainable industrial processes. The plan of action focuses upon five areas:

- Entrepreneurship in life sciences
- Simplification of the laws and regulations in this area
- Consolidation and improvement of the knowledge basis with focus and mass
- Strengthening international networks
- Communication

Economic indicators from the life sciences sector will be analysed on an annual basis from the first half of 2005 onwards. The Ministry of Economic Affairs and our agency, Senter, will also be evaluating the effects of the policy. Based on this, we shall update and adjust our policy if necessary. As the first three points, entrepreneurship, simplification of regulations and improvement of the knowledge basis, are of most concern here they will be discussed further.



### **Action plan life sciences**

#### Entrepreneurship:

- transition bio --> technopartner
- valorisation network & facility sharing for production

#### Regulatory framework

- simple procedures
- less regulations
- monitoring administrative costs

#### Science base

- genomics initiative + BSIK
- innovation in key areas (food, genomics & drugs)?

### **Entrepreneurship**

The challenge here is to ensure that the continuity of networks and the activities built up with Biopartner are maintained in the future. The current initiatives, for example, networks arising around the Biopartner centres, can submit new suggestions to Technopartner. The sum of 25 million euros is available for this program in 2005 and this amount is raised to 35 million euros in 2006. The Biopartner budget was nine million euros per year. We do not think that new incubator buildings are necessary; current capacity appears to be sufficient in practice. As incubators represented 25% of the Biopartner budget, we expect that there is sufficient room within Technopartner for new life science initiatives for start-up companies. One improvement is the seed facility in Technopartner, aimed at the promoting of start-up capital for new businesses. Investments up to 2.5 million euros are being promoted. This tool is the ministries response to the current scarcity on the risk capital market, in particular for growing starters. Technopartner will be officially launched in Amsterdam on 28 October 2004; Biopartner will be concluded on 2 November 2004 during the BIONale event in Maastricht.

The life sciences action plan also gives special consideration to the setting up of a network of expertise, which is actually an action plan for the development of an assessment network for valorisation. Next to this the life sciences action plan gives consideration to a fund to finance production equipment for life science businesses that already have products further down the pipeline. This fund can work based on the Mibiton concept, a facility-sharing foundation, that showed its value in recent years.

### **Laws and regulations**

Laws and regulations are given much consideration in our policy, as many people point to these as major factors that hinder innovation. In a constructive co-operation between the involved ministries progress is made to improve this. The Ministry of Economic Affairs can only intervene, as it is not responsible for legislation, except for the area of patents.

### **An excellent knowledge basis**

Fundamental knowledge is of great importance to the life science industry as a source for research and human capital. The necessary focus has been made in the areas of nutrition and genomics but not yet in the case of human health and medicine. Is this an unexplored area? The so-called 'smart mix' annual budget of fifty million euros can be used for new initiatives. The starting points in this regard are: research at top international level as well as financial and managerial involvement of Dutch industry.

### **Pharmaceutical research in the Netherlands**

Medical research in the Netherlands enjoys a high reputation worldwide. The Netherlands has a number of prominent academic hospitals, academic research institutes and academic research groups. I would for example, point to research into cardiovascular diseases, cancer and work carried out in the area of vaccines. Foreign multinationals enjoy carrying out clinical research in the Netherlands and co-operating with Dutch universities. However, the question is whether we are allowing foreign businesses to access the knowledge too easily, thereby passing up possible opportunities for Dutch industry. Research into medicines is expensive and takes a long time. The management of costs for research and development are high on the agenda for pharmaceutical businesses. This applies to major multinationals but also certainly to smaller players. One of the ways to manage these costs is public-private co-operation. Although FIGON has done a lot of work here, co-operation between universities and industry in the area of medicine is quite weak or at least not very visible. Attempts have been made in the past but these have not led to a public-private cooperation agreement. As mentioned earlier: a lot of research is carried out in the Netherlands but this leads to little innovation, materialized in new drugs, diagnostics or vaccines. We spend many euros upon research but do we convert enough research back into euros again?

Is the search for a drug-innovation approach with focus and mass an illusion or a challenge? Two aspects will play a role here. The Dutch businesses and universities have not yet managed to formulate focal points of joint innovation in this field and the Dutch government has policy on regulation and reimbursement for medicines, that is not at all stimulating innovation. The first challenge is therefore to formulate focal points of innovation. We will need a balanced research portfolio in the area of pharmaceuticals and be aware of making this too extensive. Can we find an excellent research portfolio in niches of the international market, which are relevant for the Netherlands? If this is the case, maybe this portfolio brings us to a public private strategy for drug development and to a TTI in this area. As for the second challenge: The Dutch pharmaceutical market (as in most other countries) is strictly regulated. The government determines which medicines are allowed on the market and how much should be paid for it. I often hear this reimbursement system does not stimulate innovation. The Ministry of Economic Affairs should therefore consult with the Ministry of Health, Welfare and Sport to see if the reimbursement system can

be made innovation-friendly. A possibility is to reserve a small part of the medicine budget for new innovative medicines, preferably developed by smaller businesses. An example of this is the American SBIR approach. This is a Small Business Innovation Research fund for early stage research and development efforts of a high-risk nature that may have excellent commercial potential. In this approach part of the government's research budget is used for stimulating innovation in industry. The recent 'Industry Letter' points out this possibility. Another possibility is to formulate a joint innovation strategy with a good synergy by both ministries.

Strategic consultation between the Ministry of Economic Affairs, the Ministry of Health, Welfare and Sport, industry and universities in order to create a stimulating climate for innovation is most likely to succeed if we have a concrete and focussed plan for a focal point for drug innovation. If this thinking results in a realistic proposal, the Ministry of Economic Affairs would be pleased to work on it.



## The Drug Research Academy – a Danish case study

The Danish pharmaceutical industry constitutes a substantial part of the Danish economy, with extensive research, substantial exports and strong growth in investment and employment. Today the pharmaceutical industry has more than 26,000 employees and exports worth more than 4.5 billion euros, corresponding to approximately 8% of total Danish exports. The pharmaceutical industry accounts for a third of all industrial research and development activities in Denmark, which makes it the most innovative sector in the country's economy. Thus, education, training and research in the pharmaceutical sciences at a high level are important for the future development of the pharmaceutical industry in Denmark. In the end this will have a positive effect on the patients and, eventually, on society.

The pharmaceutical sciences are currently undergoing rapid development and major restructuring. The revolution of molecular biology and progress in mapping the human genome have created new challenges and opportunities for drug research covering all aspects from discovery to clinical use of drugs. To meet the challenges, there is a pressing need for pharmaceutical scientists with interdisciplinary training coupled with an academic and industrial research perspective.

This task cannot be assumed either by the Danish universities or by the pharmaceutical industry alone. Progress calls for the collaboration of all parties involved in drug research and development including health care professionals in hospitals, universities, regulatory authorities, industry and public funding bodies. The Danish government has a key interest in exchanging knowledge and technology between universities and industry. The Danish Ministry of Science, Technology and Innovation has stated it several times: the Danish government wants to open a four-lane highway between the universities and industry.

### The Drug Research Academy

One of the initiatives, which have been taken to meet these demands, is the establishment of the industry-oriented research school, The Drug Research Academy (DRA) at the Danish University of Pharmaceutical Sciences (DFU). The DRA was established in 2002 and covers a seven-year programme. The overall objectives of the Drug Research Academy are:

- To strengthen post-graduate education and make the training of pharmaceutical scientists interdisciplinary, with an international focus and with an industrial perspective.
- To strengthen research at the DFU.

- To train highly qualified pharmaceutical scientists in core disciplines related to drug discovery and development.
- To continuously develop ‘state of the art’ graduate courses within pharmaceutical sciences.
- To make the DRA an internationally recognised graduate school within the area of pharmaceutical sciences.
- To increase the interest of junior pharmaceutical scientists in conducting research within universities and industry.

The Drug Research Academy covers all core disciplines related to the drug development process from discovery to clinical use, and is the largest research school with industrial orientation in Denmark. The DRA is coordinated by the Danish Association of the Pharmaceutical Industry, the Danish Medicines Agency, and the Danish University of Pharmaceutical Sciences. The organisation of the DRA consists of a board in which top management of industry is strongly represented.

The DRA is co-financed by the Ministry of Science, Technology and Innovation and ten Danish pharmaceutical companies including three biotechnological companies. The DRA’s budget of approximately twelve million euros covers more than forty PhD grants and about eleven three-year post-doctoral grants. The external partners and the Ministry of Science, Technology and Innovation each finance approximately one third of the total budget. The remaining third is funded by DFU directly by including ordinary PhD fellowships in the programme.

In order to achieve the objective of strengthening the integration of research activities at DFU and relating these activities to the pharmaceutical industry, DFU has identified four key areas as part of the focus process. This enables us to create synergies between individual departments. The four selected strategic areas are:

1. structure-based drug research
2. metabonomics
3. drug delivery and formulation design
4. rational pharmacotherapy

This means that PhD projects must primarily be related to topics covered by these areas, a key element in the objective of DRA to further develop the concept of an integrated research training programme. As a result, the research training meets the challenge of allowing the PhD student to complete a focused, limited research project while at the same time gaining solid knowledge of related fields. For this purpose, PhD students within the DRA are expected to collaborate with other scientists on complementary research projects.

### **Industrial PhDs**

The DRA’s PhD projects are industry-oriented. The PhD projects are directed towards research questions in the company. It is a partnership between a company, a university and a PhD student. The industrial PhD education programme encompasses a full PhD degree and an Industrial PhD title on top of that. The industrial PhD name is a brand name, which denotes innovation and scientific dedication. There are about 70 PhD projects offered every year and the industrial PhD students account for 5% of the 5,000 active PhD students in Denmark. The differences between an industrial PhD and a traditional PhD are:

## Industrial PhD vs. traditional PhD

### *Traditional PhD:*

- Research project
- The application is approved by the university
- Six months courses (30 ECTS points)
- Employed at the university
- It is recommended that the student spends approx. six months at a foreign university
- 800 hours' teaching and dissemination of research results

### *Industrial PhD:*

- Research in issues relevant to private enterprises
- Application approved by the university and the Ministry
- Six months of PhD courses (30 ECTS) plus the mandatory Industrial PhD course
- Employed in a business, but studying half the time at the university
- It is recommended that students attend courses at foreign universities
- 800 hours' dissemination of research knowledge

A PhD student at the DRA normally has one main supervisor and two co-supervisors. One of the co-supervisors will typically be a junior scientist from the research group at DFU whose research expertise is central to the PhD project. The other co-supervisor is a scientist employed with the company that is co-financing the project. The PhD projects are mostly not in the core interest of the company that is sponsoring the project, but they are of general interest and have an educational purpose. This combination of supervisors and a three to six months research placement in industry ensures that the PhD student gains an insight into and experience with both academic and industrial research. Participation in a number of PhD courses is a compulsory part of the research training. The course programme must comprise courses that contribute to the PhD student's theoretical and experimental knowledge. The programme should contribute to the student's skills in connection with the chosen project as well as giving the PhD student a good understanding of related research areas of possible importance to the establishment of research collaboration in relation to the PhD project. Training on the PhD courses is to a large extent conducted by internationally recognised scientists, and participation in the courses is vital to the internationalisation of the DRA. Participation in two of the five compulsory courses is required. Non-pharmaceutical candidates must also attend the 'Industrial Drug Development' course at the DFU. All PhD students must attend a total of six PhD courses. In cooperation with the DFU, the DRA offers a total of fifteen PhD courses, and as the pharmaceutical sciences are currently undergoing rapid development, courses will regularly be added to the curriculum.

## **Contract**

The DFU and the external partners have agreed on a generalised standard contract covering all kinds of legal issues.

We give the right of first refusal to the company when an invention has been produced within the project. Most of the agreements state that the major part of the thesis will be publicly available, it is after all a public defence. If the parties in the cooperation agreement have agreed upon an 'option' and/or a 'right of first refusal' to inventions resulting from the cooperation then the terms and conditions of such exploitation of the invention must be agreed upon in a separate agreement between the parties. The considerations/payment agreed upon in the agreement must reflect the contribution of the parties to the project. No strict numbers are pursued at this early stage because it is not known where the project will end, if any patent will result from the project or if the research efforts will eventually pay off. This generalised standard contract is the basis for the collaboration and the negotiation of the final contract. The parties are obliged to enter into those negotiations in good faith and the negotiations must contain an agreement on the consideration to the DFU for such use. This standard contract makes it possible to shorten the negotiations to three to four weeks for a contract for a specific programme. No PhD project will be started without a contract signed by industry.

### **Matters to be regulated in a standard contract**

- Publication policy.
- Intellectual property rights.
- Confidentiality policy.
- Distribution of rights.
- Negotiation, procedures and considerations.
- Cooperation agreement concerning Ph.D projects.
- Rights to results: 'option' and/or a 'Right of first refusal'.
- Terms and conditions: 'The main part of the thesis must be publicly available'.
- Deviations from the general terms and conditions for a cooperation with DFU.

## **Conclusions**

The DRA builds on a mutual acceptance and understanding of the differences in objectives and expertise between universities and industry. An important feature of the cooperation is that it is built on agreements. The objectives are to educate highly qualified pharmaceutical PhDs for innovative, industrial research groups, to strengthen the research at the DFU and to further develop concepts for an integrated research education programme.



# Samenvatting discussie workshop 1

## **Fundamenteel geneesmiddelenonderzoek: *target finding, drug discovery en drug delivery***

### **Discussiestelling 1**

*De zwakte op het terrein van geneesmiddeleninnovatie in ons land ligt met name in het ontbreken van een lange termijnstrategie daarvoor bij de overheid.*

Er is sprake van een paradox in de technologieontwikkeling in Nederland: de mogelijkheden tot echte innovatie leveren veel nieuwe kansen op, mede te danken aan een veranderde opstelling van universiteiten en industrie, maar de doelstellingen worden niet ten volle benut. Op welke manier kan men in Nederland de nog bestaande barrières wegnemen en deze paradox aanpakken? Op dit gebied is voor de overheid een veel sterkere faciliterende rol weggelegd.

Ten eerste moet er meer duidelijkheid komen over de sterke en zwakke kanten van het nationale geneesmiddelenonderzoek. De grotere bedrijven zijn tegenwoordig geneigd zich uit Nederland terug te trekken en dat terwijl het volume van de Nederlandse farmaceutische industrie al niet erg groot was. De kleinere farmaceutische bedrijven vertonen daarentegen wel de potentie tot groei. Zwitserland is een klein land met een zeer omvangrijke farmaceutische industrie. Die is gerealiseerd door de aanwezigheid van adequate financiële middelen, de juiste mensen met de juiste ideeën en een goede organisatie. Met deze eigenschappen wordt een land ook aantrekkelijk voor buitenlandse bedrijven.

Ten tweede moet Nederland duidelijker kiezen voor een beperkt aantal relatief sterke onderzoeksgebieden binnen de geneesmiddelontwikkeling. Hiervoor is een cultuuromslag noodzakelijk. Men zou de gebieden kunnen classificeren op therapeutische speerpunten en essentiële technologische ontwikkelingen. De keuze voor deze gebieden moet goed doordacht zijn en zowel de industrie als de universiteiten moeten haar ondersteunen. Bij deze keuzen moeten de partijen wel rekening houden met de onderzoeksprogramma's van de farmaceutische bedrijven en de universitaire groepen: als succes op de korte termijn uitblijft kunnen zij niet direct van onderzoeksrichting veranderen. Geld is een belangrijk middel om deze focusring te sturen: onderzoeksgroepen binnen de gekozen gebieden moeten aanvullende financiële middelen ontvangen. Alleen dan wordt het gewenste speerpuntbeleid voortvarend ingevoerd.

Ten derde moet het Nederlandse veld vaststellen wat het over vijf tot tien jaar op dit terrein bereikt wil hebben. De universiteiten, de overheid en het bedrijfsleven

moeten tot een gezamenlijke lange termijnstrategie komen. Tot het bedrijfsleven behoren niet alleen de bekende grote bedrijven, maar ook de vele kleine *start-up* bedrijven die recentelijk een rol zijn gaan spelen. Binnen de industrie is al een verandering zichtbaar: terwijl bedrijven eerder steeds nieuwe reeksen stoffen ontwikkelden voor een bepaalde indicatie, identificeert men nu steeds vaker nieuwe doelwitten (*targets*) waarop men vervolgens de verdere geneesmiddelontwikkeling baseert. Deze ontwikkeling is noodzakelijk, maar zeer kostbaar. Het gevaar bestaat dat de overheid de benodigde *extra* bekostiging van geneesmiddelenonderzoek voornamelijk zal realiseren door middelen weg te nemen uit de eerste geldstroom. In het verleden bleek al dat de kwaliteit van de basale universitaire infrastructuur hierdoor nadelig beïnvloedt werd. De overheid kan een meer positieve rol spelen bij de vergoedingssystematiek van geneesmiddelen. In de vergoedingen moet men de kosten van het totale ontwikkelingsproces betrekken. In het algemeen dient de overheid het tweerichtingsverkeer tussen universiteiten en industrie meer te faciliteren. Goede voorbeelden zijn de Biopartner- en STIGON-programma's van het ministerie van Economische Zaken.

Ten slotte is een grotere inbreng van dit wetenschapsveld in de politiek mogelijk. De vertegenwoordiging is op dit moment zeer mager. Daardoor heeft de farmaceutische wetenschap geen adequate inbreng in de gremia waar de beslissingen worden genomen.

## **Discussiestelling 2**

*Alleen door een krachtige gezamenlijke actie van universitaire en industriële onderzoeksteams en de betrokken ministeries kan ons land internationaal een vooraanstaande rol in het farmaceutische onderzoek en de farmaceutische productie verwerven.*

Europa moet op korte termijn haar krachten bundelen om de competitie met bijvoorbeeld de Verenigde Staten, Japan en de opkomende landen als India en China niet te verliezen. Daarvoor moet allereerst de in Nederland aanwezige kwaliteit bij elkaar worden gebracht. Ondanks het doorgaans grote enthousiasme voor samenwerkingsacties is dit nog niet structureel gerealiseerd. In het gehele veld vindt bijvoorbeeld nog te weinig uitwisseling plaats van mensen, hoewel men binnen de universiteiten wel initiatieven neemt om deze uitwisseling te bevorderen. Competitie, ook tussen de universiteiten, kan hierbij contraproductief zijn. Competitie bewerkt echter wel een hogere kwaliteit en is dus niet per definitie nadelig, zolang het maar niet leidt tot non-productiviteit en verlies van kennis. Om samen te werken moeten zowel universiteiten als industrie open zijn over hun problemen. De samenwerking moet op de werkvloer beginnen, bij de betrokken wetenschappers die samen een missie nastreven of elkaar gewoon helpen met hun kennis en/of infrastructuur. Verder moet de samenwerking niet alleen gericht zijn op technologieën of op de markt, maar ook op kansen tot wetenschappelijke doorbraken.

Om de in Nederland aanwezige kwaliteit bijeen te brengen, hoeft het farmaceutisch veld niet opnieuw het wiel uit te vinden, maar kan het haar voordeel doen met verwante voorbeelden van Technologische Top Instituten (TTI)/ Centres of Excel-

lence zoals dat voor polymeren en het Voedingsinstituut in Wageningen. Een succesvolle samenwerking tussen industrie en universiteiten met een duidelijke rol van de overheid is ook gerealiseerd in het NWO-project Advanced Catalytic Technology for Sustainability (ACTS). Deze successen zijn helaas bij te weinig mensen bekend. Kleine bedrijven vormen een wezenlijk onderdeel van de Nederlandse farmaceutische industrie. Evenals de grotere bedrijven kunnen ook de kleine *start-up* bedrijven profiteren van een TTI voor geneesmiddelenonderzoek. Dat ook een kleine farmaceutische bedrijvigheid voordeel kan hebben van een TTI blijkt uit de succesvolle samenwerking van overheid, universiteit en industrie in Denemarken. Bij dit alles moet de nadruk niet teveel alleen op de technologie liggen. *Targets* en *leads* zijn en blijven de belangrijkste doelen van farmaceutisch onderzoek. Wel moet de technologie deel uitmaken van de eigenlijke vraagstelling, onder meer op de gebieden van geavanceerde voorspellende modellen en toediening van geneesmiddelen (*drug delivery*).

Een goede samenwerking wordt pas echt duurzaam als men ook in het onderwijs veranderingen doorvoert. Dit brengt de mentaliteitsverandering tot stand die kennisuitwisseling en -overdracht bevordert. De hierboven genoemde *centres of excellence* of de onderzoeksnetwerken moeten dan ook nadrukkelijk een onderwijstaak krijgen. Een deel van deze taak wordt vervuld door in de betreffende centra stageplaatsen aan te bieden. Bovendien moeten studenten ook aan de slag kunnen binnen de infrastructuur van de industrie.

### **Discussiestelling 3**

*Er dient in ons land veel meer aandacht te komen voor systematische kennisscouting, kennisbescherming en kennisexploitatie evenals tweezijdige kennis- en technologieoverdracht tussen de universiteiten en bedrijven op het gebied van geneesmiddeleninnovatie.*

Universiteiten zijn zich vaak onvoldoende bewust van de waarde van hun intellectuele eigendom. Ook op dit punt is een cultuuromslag noodzakelijk. Universiteiten zijn zelf verantwoordelijk voor een goede structuur om hun intellectuele eigendom te beschermen. Al tijdens de medische en farmaceutische opleidingen moet gewerkt worden aan het vergroten van het bewustzijn hierover. Bij de kennisbescherming in het geneesmiddelenonderzoek in Nederland kan men onder meer gebruik maken van de expertise van Biopartner. Sommige universiteiten beschikken al over een eigen octrooi/ kennistransferorganisatie, in combinatie met een regeling waarbinnen er financiële of andere drijfveren zijn voor de individuele onderzoeker. De universiteit kan haar octrooionderhoud verder bekostigen door haar octrooien tegen een redelijke vergoeding aan een geïnteresseerd bedrijf in licentie te geven.

Naast de kennisbescherming zelf moet ook de kennisscouting toenemen. Universiteiten en onderzoekers moeten alert zijn op de kennis die ontstaat bij wetenschappelijk onderzoek en op de commerciële mogelijkheden hiervan. Voor veel academici is het echter een te grote stap een octrooi aan te vragen en de uitvinding of ontdekking aan een bedrijf te verkopen. Daarom moet men dit proces in kleinere stappen

verdelen. De overheid zou dit nadrukkelijk financieel moeten ondersteunen. De geneesmiddeleninnovatie in de Verenigde Staten is bijvoorbeeld voor een belangrijk deel gebaseerd op het opmerken van goede ideeën en het uitbuiten van de mogelijkheid deze tot een product te brengen.

#### **Discussiestelling 4**

*De huidige toename in het ontwerp en de toepassing van macromoleculaire farmaca (therapeutische eiwitten, DNA/RNA constructen) vergt een gelijktijdige ontwikkeling van geavanceerde toedieningstechnologieën om deze nieuwe mogelijkheden ten volle uit te buiten.*

Tot op heden werken preklinische en klinische onderzoekers nog te weinig structureel samen, terwijl men op het terrein van de toedieningsproblematiek veel van elkaar kan leren. Op dit moment koppelt het farmaceutisch onderzoek de toepassing van nieuwe geneesmiddelen en nieuwe diagnostische technieken om op die manier de interventies met geneesmiddelen beter te monitoren. Het Nederlands farmaceutisch onderzoek is, internationaal gezien, zeer goed toegerust voor dergelijk fundamenteel geneesmiddelenonderzoek. De vaak goede klinische infrastructuur zou echter beter gebruikt kunnen worden. Voor de nieuwe diagnostische technieken kunnen onderzoekers overigens vaker een beroep doen op de aanzienlijke kennis van nanotechnologie in ons land. Ook in het onderwijs moet meer aandacht worden besteed aan de bundeling van verschillende onderdelen van geneesmiddelenonderzoek (preklinisch en klinisch). De huidige medische en farmaceutische curricula zijn te zeer versnipperd. Artsen hebben te weinig inzicht in het proces van 'molecuul tot medicijn' voorafgaand aan de therapie. In de opleiding van medici en farmaceuten moeten dus ook de huidige moleculair biologische aspecten een grotere plaats krijgen. Dit vergroot niet alleen de deskundigheid van artsen en apothekers, maar verbetert bovendien de onderlinge communicatie, ook met farmaceutisch onderzoekers. Voor dit zelfde doel is het aanbevelenswaardig artsen en farmaceuten al tijdens hun studie vaker samen te brengen.

# Samenvatting discussie workshop 2

## Klinisch geneesmiddelenonderzoek

### Discussiestelling 1

*Innovatief klinisch geneesmiddelenonderzoek zal sneller verlopen als de regelgeving afneemt.*

De ingewikkelde regelgeving op het gebied van geneesmiddelenonderzoek remt de voortgang van het klinisch onderzoek. Als er onduidelijkheid is in de regelgeving, streeft de industrie naar maximale zekerheid en hanteert zij de regels uitermate streng. De industrie kan zich op dit gebied pas soepeler opstellen, als de regels worden versimpeld. De overheid moet haar wensen omtrent regelgeving helder formuleren. Daarnaast moet regelgeving vaker worden geïnterpreteerd als regelneming. Dat wil zeggen dat onderzoekers zich actief moeten opstellen en zich voortdurend het doel van de regelgeving duidelijk voor ogen moeten houden. Instellingen moeten zelf een monitoringprogramma regelen vanwege de naderende Europese richtlijn.

Opvallend genoeg heeft bijna de helft van de Nederlandse klinische studies geen industriële ondersteuning. Een aanzienlijk deel van de klinisch onderzoekers en onderzoeksinstituten in Nederland is dus bereid studies te doen zonder de inbreng van de industrie en accepteert de regelgeving, en alles wat daarbij komt kijken. De Centrale Commissie Mensgebonden Onderzoek (CCMO) constateerde zelfs dat het aantal studies in Nederland, in ieder geval voor fase I- en II-onderzoek, licht is toegenomen.

### Discussiestelling 2

*De industrie bepaalt het klinisch geneesmiddelenonderzoek in Nederland.*

Klinisch geneesmiddelenonderzoek in Nederland wordt deels bepaald door de industrie. Voor academisch onderzoek zijn niet altijd voldoende financiële middelen beschikbaar. Samenwerking met de industrie kan dan uitkomst bieden. Dit hoeft niet schadelijk te zijn voor het onderzoek en kan zelfs een positieve uitwerking hebben. Onderzoekers moeten zich bij een samenwerking met de industrie wel actief opstellen. Samenwerking is prima, zolang de onderzoeker een participant blijft, invloed kan hebben op de studie en verantwoordelijk blijft voor het onderzoek. De individuele inzet van onderzoekers moet leiden tot een volwaardig samenwerkingsverband met universiteiten en industrie als gelijkwaardige partners. Een goede samenwerking is alleen mogelijk als beide partijen hun belangen en gemeenschappelijke doelen goed vastleggen.

### **Discussiestelling 3**

*Nederland heeft een uitstekende infrastructuur, 'is een ideaal aquarium', voor klinisch onderzoek. Deze infrastructuur wordt echter niet goed benut.*

De bestaande infrastructuur zou intensiever benut moeten worden. Men kan de informatie bijvoorbeeld toegankelijker maken door de medische dossiers van huisartsen en apothekers te koppelen. De mogelijkheden hiervoor bestaan in Nederland al en men onderneemt reeds concrete stappen in deze richting. In de academische instituten moet een infrastructuur komen, los van de individuele onderzoekers. Nu valt de bestaande infrastructuur vaak weg zodra een onderzoeker vertrekt.

De opleiding voor artsen zou meer biotechnologisch onderwijs moeten aanbieden. Ook zou men de multidisciplinaire inbreng in de studies kunnen vergroten, bijvoorbeeld door de belangrijke inbreng van bijvoorbeeld biotechnologen en statistici. Verder moet men (klinische) onderzoekers een interessant carrièreperspectief blijven bieden.

### **Discussiestelling 4**

*Industrie en klinische onderzoekers moeten samenwerken om goedkopere, meer individugerichte medicamenteuze behandelwijzen te ontwikkelen*

Om meer op het individu gerichte medicamenteuze behandelingen te ontwikkelen zijn in eerste instantie kleine studies met lage aantallen patiënten vereist. Dat betekent echter niet dat het onderzoek goedkoper zal worden. De ontwikkeling van op het individu gerichte medicamenteuze behandelwijzen vereist namelijk een andere aanpak dan het huidige onderzoek. Internationale samenwerking zal een grotere plaats innemen en onderzoekers zullen andere meetmethoden en statistische benaderingen moeten ontwikkelen. Ook zal men andere samenwerkingspartners moeten aantrekken. Zo kunnen patiëntenorganisaties een constructieve partner zijn in samenwerkingsverbanden en bijdragen aan een goed verloop van studies. Ook registratieautoriteiten, waaronder het Centraal Bureau voor Geneesmiddelen Registratie (CBG), hebben interesse in samenwerking. Onderzoekers kunnen al in een vroege fase van het klinisch onderzoek met hen overleggen over de opzet van een studie, met inachtneming van de wens om kleinere aantallen patiënten te gebruiken.

### **Discussiestelling 5**

*De industrie verricht alleen onderzoek in landen waar een grote markt is of waar onderzoek goed en goedkoop kan worden uitgevoerd. Nederland (Europa) vist zo achter het net.*

De industrie verdwijnt niet volledig naar landen met een grote markt of naar lage-lonenlanden. Dat blijkt uit de (geringe) toename van het aantal fase I en II klinische studies in Nederland de afgelopen jaren, zoals aangetoond door de CCMO. Vertegenwoordigers van de industrie zelf zijn echter niet erg positief; voor farmaceutische bedrijven wordt het uitvoeren van (delen van) klinisch onderzoek in Nederland

steeds moeilijker. De farmaceutische industrie moet onvermijdelijk uitwijken naar lage-lonenlanden om de kosten van klinisch onderzoek te beperken. Zodoende vindt een uitstroom plaats van onderzoek uit Nederland. Nederland verricht weliswaar op verschillende gebieden goed klinisch onderzoek, bijvoorbeeld in de oncologie en het cardiovasculaire onderzoek, maar kan dit kennelijk onvoldoende duidelijk maken aan het farmaceutisch bedrijfsleven. Uiteindelijk bepaalt de benodigde financiering waar klinische studies plaatsvinden en niet de kwaliteit van het onderzoek. Nederland moet zich beter verkopen.

In Europa wordt te weinig geïnvesteerd in innovatie. Mede daarom vestigen Amerikaanse bedrijven zich niet in Europa. Academische instellingen kunnen zo steeds moeilijker zelf de coördinatie van een studie in handen houden. Deze vindt steeds vaker plaats in landen als de Verenigde Staten. Een manier om onderzoek in Nederland te houden is het verbeteren van de onderzoeksinfrastructuur, zoals besproken bij de derde stelling. Ook moet de uitvoering van de klinische studies goedkoper worden.

# Samenvatting discussie workshop 3

## Technology transfer: profijt van kennis; quitte of dubbel?

### Discussiestelling 1

*De noodzakelijke infrastructuur voor het beschermen en exploiteren van intellectueel eigendom is bij universiteiten onvoldoende aanwezig.*

Universiteiten kunnen hun intellectueel eigendom vaak moeilijk beschermen. Daarom komen de opbrengsten van een stof, die mede door een academische onderzoeksgroep is ontwikkeld, grotendeels terecht bij het farmaceutisch bedrijf dat van de stof een bruikbaar geneesmiddel heeft gemaakt. Universiteiten moeten dus beter waken over hun kennis en hoewel een aantal universiteiten in Nederland een regeling voor kennisbescherming heeft, kunnen universiteiten in het algemeen moeilijk beschikken over de hiervoor benodigde expertise. Het traject om zelf het octrooi te exploiteren is te kostbaar voor een universiteit dus zou de kennis, waarop een octrooi is aangevraagd, na een jaar of twee de universiteit moeten verlaten, bij voorkeur in de vorm van een *start-up* bedrijf of verkoop aan een groter farmaceutisch bedrijf. Om dit proces soepeler te laten verlopen moeten academische instellingen zich meer bewust worden van het belang van octrooien. Dit kan niet zonder een culturomslag binnen de universiteiten.

Moet de academische kennisbescherming landelijk, of per universiteit georganiseerd worden? De workshopdeelnemers geven de voorkeur aan één ondersteunend technologieovernamecentrum per universiteit. Een dergelijke structuur kan vrij gemakkelijk aansluiten op de al bestaande infrastructuur binnen universiteiten. Deze organisatie moet zo dicht mogelijk bij de werkvloer staan en gebaseerd zijn op directe persoonlijke contacten. De lokale eenheden die zo per universiteit ontstaan, moeten goed met elkaar blijven communiceren. Deze kleine groepen moeten zich pro-actief opstellen, scouten, voorlichting geven aan onderzoekers over de bescherming van het intellectuele eigendom en snel actie ondernemen bij een nieuwe uitvinding of ontdekking. Obstakels voor de invoering zijn de financiering en personele bezetting van een dergelijke organisatie per universiteit. Waarschijnlijk kan een dergelijk stelsel pas bestaan bij een forse hoeveelheid bruikbare octrooien. Daarom zal een aanzienlijke voorfinanciering nodig zijn. Het zal bovendien relatief lang duren tot de revenuen hiervan binnenkomen. De overheid vindt het belangrijk onze kennis binnen de grenzen te houden. Het Ministerie van Economische Zaken zou daartoe een nationaal financieringssysteem voor patenten kunnen opstarten om in de benodigde financiering te voorzien.



## **Discussiestelling 2**

*Duidelijkheid vóóraf over de verdeling van eventuele financiële opbrengsten van kennis is dringend gewenst en zal de kenniseconomie in Nederland stimuleren.*

Voorafgaand aan onderzoek zouden de partijen afspraken moeten maken over de verdeling van eventuele financiële opbrengsten en de bescherming van het intellectuele eigendom. Om te voorkomen dat men voor ieder nieuw onderzoek lange onderhandelingen moet voeren, zou men een algemeen contract kunnen opstellen dat als basis dient voor alle universiteiten. De specifieke afspraken kunnen dan worden vastgelegd in een bijlage van het contract. Als industrie en universiteit op tijd afspraken maken hoeft het aanvragen van een octrooi niet te botsen met een publicatie in een wetenschappelijk tijdschrift.

Het gebeurt bij universiteiten vaak dat werknemers die een eigen bedrijf beginnen kennis meenemen en exploiteren. Hier zou men een zelfde regeling kunnen invoeren als in het bedrijfsleven, namelijk dat onderzoekers bij hun aanstelling een convenant tekenen met de universiteit, waarin de afspraken hierover zijn vastgelegd. Ook is er een cultuuromslag nodig: wetenschap wordt business. Universiteiten moeten echter geen kennisfabriek worden. Dit strookt niet met de missie van de universiteiten en bedreigt de geloofwaardigheid van de wetenschap in de samenleving.

## **Discussiestelling 3**

*Voor continuïteit in de samenwerking tussen universiteiten en bedrijven is het noodzakelijk dat er bij de industrie begrip bestaat voor fundamenteel onderzoek en dat onderzoekskeuzes niet te zeer worden ingegeven door korte-termijn marketingoverwegingen.*

Een goede samenwerking is alleen mogelijk als beide partijen een gemeenschappelijk doel en/of interesse hebben, bijvoorbeeld een gedeelde interesse in fundamenteel onderzoek of de educatie van wetenschappers, als de partijen gebruik maken van elkaars kundigheid en als ze elkaar als gelijkwaardige partners beschouwen. Beide partijen moeten begrip hebben voor de soms verschillende wederzijdse belangen (zoals bijvoorbeeld de noodzakelijke tijdelijke geheimhouding van een ontdekking en de wens om deze snel te publiceren). Continuïteit in de samenwerking is belangrijk, maar kan niet worden afgedwongen. Omdat het gehele ontwikkelingstraject van een geneesmiddel al gauw vijftien jaar duurt, is het praktisch niet mogelijk om, de samenwerking voor deze hele periode contractueel vast te leggen. Wel kunnen de partijen afspraken maken over delen van het onderzoek. Een samenwerkingsovereenkomst over een periode van drie tot vier jaar is niet ongebruikelijk. Deze samenwerking is deels gebaseerd op wederzijds vertrouwen, deels is het een kwestie van goede afspraken maken. Universiteiten zouden iemand kunnen aannemen om de afspraken met de industrie te verzorgen. In de industrie moeten tegelijkertijd mensen werken die gevoel hebben voor de waarden van fundamenteel onderzoek.

#### **Discussiestelling 4**

*Het winstgevend maken van kennis door middel van het opzetten van spin-off bedrijven is een goede manier om economisch rendement uit kennis te halen. Gezien de onervarenheid van wetenschappers om te opereren als ondernemer is professionele ondersteuning van deze aanpak in Nederland noodzakelijk.*

Over de voordelen van *spin-off* bedrijven bestaat geen enkele twijfel. Het is echter de vraag of de opbrengsten van deze bedrijven ook weer bij de onderzoeksgroep in kwestie terugkomen, zodat deze in nieuw onderzoek kan investeren, of dat het geld terugvloeit naar het *spin-off* bedrijf zelf. Dit is een van de noodzakelijke afspraken in een algemeen contract.

Veel starters hebben te hoge verwachtingen als zij een eigen bedrijf beginnen. Vaak blijkt dat ondernemen niet bij alle wetenschappers in het bloed zit. Daarom moeten wetenschappers, die een eigen bedrijf willen opzetten, daarbij iemand betrekken met verstand van ondernemen. Zo moet er een marktanalyse plaatsvinden, en als de onderneming daadwerkelijk wordt opgestart, zal iemand haar draaiende moeten houden. Vaak beschikken dergelijke bedrijven over onvoldoende startkapitaal. De overheid zou hierin meer kunnen faciliteren. Een goed voorbeeld van de juiste ondersteuning voor *spin-off* bedrijven is het netwerk van deskundigen van Biopartner. Biopartner wordt echter eind 2004 opgeheven.

#### **Discussiestelling 5**

*Selectieve financiële ondersteuning van succesvolle langlopende samenwerkingsverbanden tussen universiteit en industrie door de overheid zal het profijt van kennis zeer ten goede komen.*

Bij een succesvolle samenwerking tussen universiteiten en bedrijven, zeker over een langere periode, is selectieve financiële ondersteuning niet nodig.

# Samenvatting discussie workshop 4

## Financiering van geneesmiddelenonderzoek in de klinische fase

### Discussiestelling 1

*Het is te betreuren dat er in Nederland weinig aandacht is (geweest) voor de betekenis van basaal farmaceutisch onderzoek (geen: NWO-stichting, topinstituut, Bsik-subsidie). De vraag naar de oorzaak van de situatie is minder interessant dan de vraag hoe er verandering in te brengen.*

Nog steeds lijkt de Nederlandse overheid zich onvoldoende bewust van het belang van farmaceutisch onderzoek; het Innovatieplatform heeft sleutelgebieden vastgesteld, maar een sleutelgebied gezondheid ontbreekt. Toch is de handel in Nederlandse geneesmiddelen groter dan die in tulpen, en bloemen vormen wel één van de sleutelgebieden. De ministeries van Economische Zaken en Onderwijs, Cultuur en Wetenschap kozen innovatie als één van hun speerpunten. Hiervan kan de farmaceutische sector, zowel industrie als wetenschap, profiteren, maar daarvoor moet ze zich beter organiseren. De farmaceutische wereld moet met een voorstel komen dat de betekenis van basaal farmaceutisch onderzoek verduidelijkt. In dit voorstel is focusering belangrijk, maar men moet ervoor oppassen dat goede ideeën, die buiten deze focusering vallen, geen kans krijgen.

### Discussiestelling 2

*Samenwerking tussen industrie en universiteiten leidt slechts tot optimale resultaten wanneer de deelnemers aan die samenwerking voldoende op de hoogte zijn van het specifieke karakter van de andere organisatie (doelstelling van onderzoek; geheimhouding; geen researchopdrachten).*

De samenwerking tussen de publieke en de private sectoren is in Nederland de afgelopen jaren niet goed van de grond gekomen. Het Deense model (zie de lezing van S. Frøkjaer) is een goed voorbeeld hoe productieve interactie tussen industrie en universiteiten anders kan plaatsvinden. In Nederland blijft het financiële belang, inherent aan de werkzaamheden van de industrie, een lastige kwestie voor academische instellingen. Universitair onderzoek moet immers waardevrij blijven. Aan de andere kant accepteert de industrie geen academische inbreng in het eigen onderzoek. Beide partijen moeten hun instelling aanpassen, om tot een goede samenwerking te komen.

### **Discussiestelling 3**

*Octrooiaanvragen door universitaire groepen zijn alleen zinvol als er voldoende aandacht is voor de exploitbaarheid van de uitvinding (in vivo experimenten; routineonderzoek; bekostiging).*

De opbrengsten van onderzoek door een universitaire onderzoeksgroep moeten op de één of andere manier weer terugvloeien naar die onderzoeksgroep. Hiervoor moet bij universiteiten een cultuuromslag plaatsvinden.

### **Discussiestelling 4**

*De aanwezigheid – in een land – van een succesvolle farmaceutische industrie is van levensbelang voor universitair, basaal onderzoek; sterke universitaire groepen op hun beurt zijn een voorwaarde voor het succes van die industrie (opleiding; exploratie van wetenschap; hoogspecifieke expertise).*

In het verleden bleek herhaaldelijk dat het de universitaire ‘uitvinder’ niet lukt zijn uitvinding succesvol op de markt te brengen. Hiervoor is de inbreng nodig van de farmaceutische industrie. Maar aan de andere kant heeft academisch onderzoek ook vaak uitgangspunten aangedragen, die vervolgens door de industrie in succesvolle medische toepassingen zijn omgezet. Om de voorgestelde samenwerking op termijn goed te laten verlopen moet men beginnen bij het onderwijs. De artsopleidingen moeten worden aangepast, door de onderzoekscomponent hierin te vergroten.

In plaats van reeds bestaande organisaties en infrastructuur te ondersteunen, moeten de partijen in Nederland iets geheel nieuws opzetten. Nederland heeft behoefte aan een organisatie die het gehele traject van geneesmiddelenontwikkeling omvat en zich tevens sterk maakt voor verkorting van dit traject. Verder kan deze nieuwe organisatie zich bezighouden met ideeën van (pre-)klinische onderzoekers in de academische wereld waarvoor nu geen financiering beschikbaar is, of met onderzoek dat voor de industrie absoluut niet rendabel is, zoals onderzoek naar weesgeneesmiddelen.

Dat dit symposium georganiseerd is en de hoge opkomst op deze dag, bewijzen dat de tijd rijp is voor nieuwe initiatieven. Het ministerie van Economische Zaken is bereid goede voorstellen te honoreren. Ook het ministerie van VWS stelt hiervoor fondsen beschikbaar.

De deelnemers aan het symposium stellen voor te beginnen met een Technologisch Top Instituut of *centre of excellence* voor geneesmiddelenonderzoek. Dit TTI zal in eerste instantie haar eigen projecten opzetten, zoals bijvoorbeeld bij weesgeneesmiddelen, met gerichte aandacht voor enkele ziektegebieden. Deze focusering kan plaatsvinden op basis van de aanbevelingen in het rapport *Priority Medicines* van de *World Health Organization*. Dit rapport categoriseert ziekten naar urgentie. Daarnaast kunnen universiteiten ideeën voor (pre-)klinisch onderzoek aan het instituut aanbieden. Deze ideeën kunnen door het instituut verder in waarde worden omgezet. Uiteindelijk kan het TTI het resultaat aanbieden aan een (groot) farmaceutisch bedrijf om het verder uit te werken. Het instituut verricht dus zelf ook onderzoek,

in ieder geval tot aan het bewijs van het principe (*proof of principle*) van een nieuw geneesmiddel. Dit instituut bevat ook kennis die voor bedrijven van belang is. De industrie kan daarvan uiteindelijk gebruik maken. Zo creëert men geld, inkomsten en werk.

Bij reeds bestaande TTI's werken veel AIO's. Het moet in dit geval echter gaan om een ontwikkelingsinstituut, niet om een opleidingsinstituut. Een dergelijk TTI zou gunstig zijn voor de financiering van geneesmiddelenonderzoek, omdat de industrie zich niet meer hoeft te wijden aan de *hit and run* –procedure. Ook zou het TTI mogelijk de marktintroductie van een nieuw ontwikkeld geneesmiddel kunnen financieren. De vraag is echter of dit reëel is. Het TTI zal voor een deel inkomsten genereren door octrooien die uit haar onderzoek zullen voortkomen. Daarnaast zal de industrie dit instituut moeten ondersteunen, ook financieel.

## Symposium programme

- 09.25 Welcome and opening by the chairman of the organising committee  
*Jan van Gijn, Utrecht University Medical Centre*
- 09.30 Basic drug research: target finding, drug discovery and drug delivery; an academic point of view  
*Daan Crommelin, Utrecht University*
- 10.00 Basic drug research: target finding, drug discovery and drug delivery; perspective from a pharmaceutical company  
*David Schenkein, Millennium Pharmaceuticals Inc., Cambridge MA, USA*
- 10.30 Clinical drug research in oncology: the interaction between university and pharmaceutical industry  
*Jaap Verweij, Erasmus University Medical Centre, Rotterdam*
- 11.30 Entrepreneurship at universities  
*Menno Horning, Dutch Ministry of Economic Affairs*
- 12.00 Clinical drug research in gastro-enterology: the interaction between university and pharmaceutical industry  
*Sander van Deventer, Academic Medical Centre, Amsterdam*
- 12.30 International drug research  
*Werner Cautreels, Solvay Pharmaceuticals, Weesp*
- 14.00 Case study Danish Research University  
*Sven Frøkjaer, Danish University of Pharmaceutical Science*
- 15.00 Workshops in Dutch  
voorzitter: professor Maurits Allesie
- Workshop 1** Fundamenteel geneesmiddelenonderzoek: target finding, drug discovery en drug delivery  
*Voorzitter: Dick Meijer, Rijksuniversiteit Groningen*
- Workshop 2** Klinisch geneesmiddelenonderzoek  
*Voorzitter: Liesbeth de Vries, Rijksuniversiteit Groningen*
- Workshop 3** Technology transfer: profijt van kennis; quitte of dubbel?  
*Voorzitter: Maurits Allesie, Universiteit Maastricht*
- Workshop 4** Financiering van geneesmiddelenonderzoek in de klinische fase  
*Voorzitter: Chris Kruse, Solvay Pharmaceuticals Nederland / Universiteit van Amsterdam*
- 16.30 Plenaire presentatie conclusies workshops en afsluitende discussie

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## Abbreviations

ACTS	Advanced Catalytic Technology for Sustainability
CARIM	Cardiovascular Research Institute Maastricht
CBG	Centraal Bureau voor Geneesmiddelen Registratie
CCMO	Centrale Commissie Mensgebonden Onderzoek
DFU	Danish University of Pharmaceutical Sciences
DRA	Drug Research Academy
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERA-NET	European Research Area
EUFEPS	European Federation of Pharmaceutical Sciences
FIGON	Federatie voor Innovatief Geneesmiddel Onderzoek/ Netherlands Federation for Innovative Drug Research
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HOVON	Stichting Hemato-Oncologie voor Volwassenen Nederland/ Dutch Haemato-Oncology Association
IP	Intellectual Property
IRB	Institutional Review Board
KNAW	Koninklijke Nederlandse Akademie van Wetenschappen/ Royal Netherlands Academy of Arts and Sciences
MP	Millennium Pharmaceuticals
RMI	Rudolf Magnus Institute
SBIR	Small Business Innovation Research fund
STIGON	Stimuleringsprogramma voor Innovatief Geneesmiddelenonderzoek en Ondernemerschap in Nederland/ Incentive Fund Program for Innovative Drug Research and Entrepreneurship in the Netherlands
TNF	Tumour Necrosis Factor
TTI	Technologisch Top Instituut/ Technological Top Institute
UIPS	Utrecht Institute for Pharmaceutical Sciences
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen/ Dutch Law on Medical Scientific Research
WBSO	Wet Bevordering Speur- en Ontwikkelingswerk