

STAKEHOLDER OPINIONS ON THE POSITION OF THE NETHERLANDS IN CONDUCTING CLINICAL DRUG TRIALS

A SWOT ANALYSIS

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List of relevant acronyms

ACRON	Association of Clinical Research Organisations in the Netherlands
AMC	Academic Medical Centre
BROK	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers
CCMO	Centrale Commissie Mensgebonden Onderzoek
CEO	Chief Executive Officer
CRA	Clinical Research Associate
CRCN	Clinical Research Centre Nijmegen
CRO	Contract Research Organisation
CA	Competent Authority
CTA	Clinical Trial Agreement
CTMM	Centre for Translational Molecular Medicine
DCTF	Dutch Clinical Trial Foundation
EC	Ethics Committee
EFGCP	European Forum for Good Clinical Practice
EMA	European Medicines Agency
ESF	European Science Foundation
EU CTD	European Union Clinical Trials Directive
EZ	Ministerie van Economische Zaken (Economic Affairs)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IND	Investigational New Drug
KOL	Key Opinion Leader
LATAM	Latin America
LSH	Life Sciences&Health
LUT	Lokale Uitvoerbaarheidstoetsing
MC	Medical Centre
MCRN	Medicines for Children Research Network
MD	Medical Doctor
METC	Medisch Ethische Toetsings Commissie
MSD	Merck, Sharp & Dohme
NHS	National Health Services
NVMETC	Nederlandse Vereniging van METCs (Dutch Association of METCs)

NVZ	Nederlandse Vereniging van Ziekenhuizen (Dutch Association of Hospitals)
PI	Principal Investigator
PR	Public Relations
PSN	Pharmaceutical Services Network
R&D	Research & Development
SMO	Site Management Organisation
SOP	Standard Operating Procedure
STZ	Samenwerkende Topklinische Ziekenhuizen (Cooperating topclinical hospitals)
SWOT	Strength, Weaknesses, Opportunities and Threats
TIPharma	Top Institute Pharma
UMC	University Medical Centre
VWS	Ministerie van Volksgezondheid, Welzijn en Sport (Public Health, Welfare and Sport)

Introduction

Traditionally, the Netherlands has been at the forefront of clinical drug research. This can be attributed to: the high level of education received by the investigators, the large number of key opinion leaders, the high standard of care, the excellent networks available for patient recruitment, the specialist centres in place and the high quality and reliability of data collection and reporting. Within a changing global clinical drug research environment with an increasing number of competitive countries, it is therefore essential to have insight into the strengths and weaknesses of the Netherlands as a clinical drug research country.

As part of this assessment, ten stakeholders participating in the Dutch clinical trial environment were interviewed on this matter through a prepared list of questions. The questions were presented in an open and general way, in order to provide the stakeholders with the opportunity to present their own priorities with respect to the assessment. The assessment was completed with specified questions to get some more in-depth information on the most relevant topics. The interviews took place at the respective stakeholders' location in August and September of 2010. The group of participants consisted of: three Medical Directors of pharmaceuticals companies, two representatives of a Phase I unit, two representatives of a CRO, two principal investigators from an academic hospital and one principal investigator from an STZ hospital.

Detailed minutes from each interview are presented in Section II of this report. These minutes are segmented into different relevant topics in order to make a comparison between the opinions of the different stakeholders. Section I presents the overall summary of the different views of the position of the Netherlands and is completed with individual interpretations and ideas.

The interviews have been used to construct a Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis. This analysis provides recommendations on how to maintain and improve the competitive position of the Netherlands in the changing clinical research environment.

SECTION I - ANALYSIS

1 Opinions per topic of different stakeholders

As stated in the general introduction, ten stakeholders from different areas of expertise in the clinical research environment were interviewed to assess the strengths and weaknesses of performing clinical research in the Netherlands. An extensive elaboration of the interviews can be found in Section II of this report, segmented into various relevant topics. The current section begins with an overall summary of the most important outcomes of the interviews per topic. This summary is based on the perceptions and experience of the interviewees based on the highest common factor and where interesting and important, completed with individual interpretations and ideas. Based on the interviews, an overall SWOT analysis was constructed on the position of the Netherlands in the field of clinical research. The SWOT section finishes with a set of recommendations, based on the stakeholders' opinions, on how to maintain and improve the competitive position of the Netherlands in the changing clinical research environment.

1.1 CA and METC approval process

CA approval process

All participating interviewees agreed that the Dutch Competent Authority (CA) approval process in the Netherlands is excellent and superior to other European countries and also the rest of the world. The process involves only a marginal assessment being made and if no objections are posed by the CA within 14 days of submission, the clinical trial is approved.

METC approval process for Phase II-IV studies

Although the METC approval process is improving in the Netherlands, it is still considered a negative aspect of the Dutch clinical trial environment by industry (CROs, biotech and pharmaceutical companies). CRO's observe that sponsors are beginning to ignore the Netherlands when selecting countries for a clinical trial. Furthermore, pharmaceutical and biotech companies observe that it is becoming increasingly more difficult to convince their head office to consider selecting the Netherlands as a country for their clinical trial. The main reason is that patient recruitment compared to other European countries (e.g. Belgium) starts too late due to the slow METC approval process. To secure the first patient in such a study is not the major concern. The main problem is that due to the long duration of the approval process, it takes too long before all sites are up and running for a trial with competitive recruitment. In many cases, the Dutch sites often do not get the chance to substantially contribute.

This delay is mainly due to local feasibility committees simply not accepting the central METC approval and instead making their own assessment of the submission documents (e.g. they are

commenting on the protocol, instead of only looking at the local feasibility and the patient information). There is however a tendency visible within METCs and local feasibility committees to try and create a more efficient procedure in order to deal with the workload and be competitive (e.g. by creating smaller committees or subcommittees).

A further reason for delay is that the preparation and collection of the required submission package is taking too much time. It has shown to be effective when industry (the initiators of a clinical drug trial) assists the investigators with this task which subsequently speed up the process.

METC approval process for Phase I studies

The METC approval process for Phase I studies in the Netherlands is very favourable. It usually takes about two weeks from submission to approval, which is fast compared to other countries such as Germany where it takes 60 days or France where it takes 21 days. In the US it can take up to 3 months to open an IND for a Phase I trial. The Netherlands is in this respect, very competitive on a global scale.

General comments

On a global scale and with respect to the type of study where a sponsor needs to include large amounts of naïve patients, the METC approval process being used as a delaying factor is apparently not the most critical one, since in China and Brazil the approval process takes substantially longer and still these countries are very popular countries with the industry in this respect. However, at a European level the Netherlands is actually surrendering their competitive position to other countries in Europe, like Belgium, which is still a country that is considered by industry on a more regular basis. Principal investigators commented that it would also be interesting to not only look at the METC approval process, but also at timelines (e.g. the time between METC approval and the first patient in the study) and in that regard identify whether there are other delaying factors in the process that should be taken into account.

1.2 Effects implementation EU CTD

Increase of bureaucracy

All participants agreed that, with the implementation of the EU CTD, performing a clinical trial in the Netherlands has become overly bureaucratic, due to the additional administrative and reporting requirements. However, this is no different from other European countries and as such does not have an impact on the competitive position of the Netherlands.

Stricter interpretation

Another aspect that does affect our competitive position is that in certain ways the EU CTD is interpreted in a stricter way in the Netherlands than in other European countries. This is particularly the case with regard to the approval requirements for paediatric trials, trials with orphan diseases and gene therapy trials. It represents a missed opportunity, since the Netherlands has an excellent network for paediatric trials (MCRN) in place and is specifically well equipped for more complex gene therapy trials.

Further harmonization METC approval process

A threat to the Phase I clinical trial environment would be the further harmonization of the METC approval process with arrangement of the process at a European level. This would result in the levelling of approval timelines and would jeopardize our competitive position. Such harmonization of the approval process would in general create further delays. It is unlikely that METCs (which are gradually beginning to accept the assessments of their Dutch colleagues) would have no problems accepting an approval provided by an METC in Hungary for example.

1.3 Standardization of clinical trial documents

Need for standardization

Principal investigators and the industry at large have indicated that the clinical trial process (and specifically the approval process) would be faster and more efficient if documents, such as the patient informed consent form and the clinical trial agreements are standardized for clinical drug research in the Netherlands.

Patient information

The patient information form is now a document that is often checked and if deemed necessary adjusted by all participating local feasibility committees separately.

Site agreements

Contract negotiations also tend to be slow, usually because hospital lawyers are not aware of the time sensitivity of clinical research. In principle, this is not typical for the Netherlands, since it is a tendency which is reflected on a global scale. However, now that the CCMO has established guidelines which require a signed clinical trial agreement at the METC submission, this creates an additional hindering factor for the Netherlands.

Initiatives

The CCMO and Nefarma are taking initiatives to standardize the patient information form and site agreements. The CCMO has posted a patient information form template on their website. Nefarma is currently finalizing a site contract template that is based on the template proposed

by the CCMO. Nefarma members have agreed upon this template (pharmaceutical and biotech companies with a subsidiary in the Netherlands) and Nefarma is now consulting with other parties in order to garner their input. Nefarma acknowledges that a standardized site agreement can only work if: there is a solid basis and support from the local pharmaceutical and biotech industry, the CRO industry and the academic and STZ hospitals, such an approach would be similar to the situation with the NHS Trust template in the UK. In the case of the UK, the NHS Trust recognizes that (local subsidiaries of) the different parties have already previously approved the template and that it is not necessary to make substantial changes to the standard template. If such a change is not implemented it is likely that US based sponsors will continue to insist on using their own templates.

1.4 Data protection

At an international level, companies located in the EU are starting to implement procedures and structures aimed at ensuring compliance with the Data Protection Directive. However, at a local level this topic does not seem to be at the top of the agenda in the Dutch clinical research environment. Of course, parties do take into consideration the data privacy requirements with respect to the patient data. But, in the Netherlands not as much attention is paid to the topic of patient information and informed consent, as for instance is paid in Germany.

1.5 The quality of clinical research in the Netherlands

Availability of quality, expertise and Key Opinion Leaders

The Netherlands is still a very appealing country for clinical trial sponsors; it has a reputation for its scientifically high quality investigators and research staff, has a wide availability of key opinion leaders, possess technical and scientific expertise and also the high quality and reliability of the data.

Scientific output and input

The Netherlands is a small country with a relatively high output: investigators are submitting many high-level publications and are well represented at important conferences. When a sponsor needs technical and scientific input on its protocol, the Netherlands is an appealing country due to the availability of expertise on the studies of a more complex nature.

Infrastructure

The infrastructure in place for performing clinical trials in the Netherlands is also very good: excellent specialist centres, good universities, a large number of useful collaborations between different organizations, useful networks and a good health care system.

In addition, communication between the pre-clinical and clinical phase in the Netherlands is outstanding.

Mentality

In general, Dutch investigators are known for their down to earth mentality and for taking the integrity of the study data very seriously. They are also willing to collaborate at an international level.

1.6 Costs

Phase II-IV trials

For Phase II-IV studies, the cost of performing a clinical trial in the Netherlands is widely comparable to similar Western-European countries such as Germany. It is more expensive than Southern-European countries, but less expensive than the UK and Nordic countries. Compared to the US, scientifically educated staff are less expensive to recruit. Lastly, compared to countries in the emerging markets (Asia, LATAM), Western-European countries, including the Netherlands, are much more expensive.

Phase I trials

Performing a Phase I trial in the Netherlands is relatively expensive (more expensive than other European countries). Because of the high level of technical and scientific expertise and the fast start-up timelines, sponsors are still willing to pay.

1.7 Recruitment and motivation of investigators

Motivation of Dutch investigators

In general, Dutch investigators are enthusiastic about participation in clinical trials, since they acknowledge that clinical trials contribute to improved healthcare. It is however, difficult to motivate an investigator who has responsibility for direct patient health care to participate in a clinical trial and has to perform a clinical trial “on the side” without any support from the hospital. Money is usually not a decisive factor in such case, as it does not remove the obstacles. Moreover, with increased regulations funding is usually required to compensate additional resources, such as research nurses, in order to deal with the administration inherent in contemporary clinical trials.

Sponsor initiated trials

Dutch investigators are in general, better equipped and more motivated for studies that require some technical and scientific input. Industry sponsored confirmatory trials are therefore usually considered less interesting by investigators because there is often little

opportunity to provide such input and seldom the possibility to publish. Some hospital departments do see the benefit of participating in this type of trial and are prepared to provide the remuneration for more interesting research. Some investigators have also tried to negotiate one or more sub-studies that are scientifically more interesting. For proof-of-concept studies, new compound trials or trials focusing on an interesting indication it proves complicated to recruit and motivate investigators. Specialists do not show enough interest in Phase IIa trials. If this does not change, there is the distinct possibility that this type of research will disappear in the Netherlands.

Key Opinion Leaders

For Key Opinion Leaders (KOLs) it tends to be easier to negotiate more interesting terms with a sponsor. It appears that KOLs are regularly not involved at the operational level of a clinical trial. The involvement of KOLs in the daily operation of clinical trials together with other investigators is considered to be important by various parties to stimulate the conduct of clinical trials.

Studies with General Practitioners

In general, Dutch general practitioners (GPs) have limited experience in conducting clinical trials.. The most likely explanation lies in the fact that the administrative burden in the regular GP practice is high so that limited time is left for the conduct of clinical trials. In addition, the logistics (e.g. ensuring that all GPs are trained on ICH-GCP) and the fragmented nature of patient recruitment are not ideal. Parties that wish to perform a GP trial can partially overcome these obstacles by providing support in the daily operations of the trial and by investing in a strong relationship with the GP. Initiatives to improve the conduct of clinical trials at the GP offices are currently ongoing. Some GP co-operations have made an effort to set up a solid infrastructure for clinical research, which is highly appreciated and supported by the pharmaceutical, biotech and CRO industries.

1.8 Training and education investigators

Education

Generally, the education of the investigators and study staff is internationally perceived to be of high quality. In order to create a setting in which more top clinical research is carried out, all players in the clinical research environment should take responsibility for the training and education of investigators and staff who have to deal with high quality clinical trials. Some parties are already providing interesting education and training opportunities related to clinical research (CHDR, Erasmus MC). Nevertheless, there is insufficient collaboration and vision on an integrated country-wide approach with respect to education of the required investigators and clinical research staff.

ICH-GCP

Investigators in the Netherlands are not always fully aware of the ICH-GCP requirements. Some investigators have a perception of the training regulations as very demanding in comparison to other types of research. The probiotics trial has exposed the reality that the Dutch clinical research environment still needs improvement with respect to ICH-GCP compliance. The possibility of providing ICH-GCP training to investigators could be fulfilled in the investigator meeting. Unfortunately, in practice the investigators tend to send their research nurses believing them to have enough experience to perform the research.

An effective initiative is the BROK-course (which was originally set up to educate academic researchers on the ICH-GCP guidelines) but is now also very popular for investigators in other hospitals. Improving research quality through better training can be used to strengthen our competitive position. The down-side at this stage is that the demand for education is bigger than the supply. A positive development here is the decision by some relevant Master course providers to make ICH-GCP part of the curriculum (e.g. Health Science at the VU).

Registration and certification

Different pharmaceutical and biotech companies do not always accept each other's ICH-GCP certificates. Their policy is often that the participating investigators need ICH-GCP training and a certificate from the relevant company or from an accredited training institute.

The difficulty in the Netherlands is that at the moment there is no system for assigning accredited training institutes and there is no central registration of ICH-GCP trained investigators. Only participants of the BROK-course are centrally registered with certificates accepted as originating from an accredited training institute. It would significantly improve conditions if the Dutch authorities would assign accredited training institutes and arrange for the central registration of trained investigators. The ICH-GCP training could be less extensive and time consuming than the BROK-course through provision of training in the form of e-learning, which, because of its efficiency also makes it easier to reach the principal investigators.

1.9 Infrastructure hospitals

Support hospital

Clinical research is usually not supported by the relevant hospital. This is particularly evident with regard to industry sponsored research: it is not considered particularly prestigious and the opinion prevails that this type of research costs the hospital money and that the investigators are the only party benefiting. In Radboud University Nijmegen Medical Centre, a hospital gratuity system is in place based on the performance of the investigators. This system

aims to create possibilities for the most successful investigators to dedicate more time to research.

Research Desks

A positive trend is the establishment of (clinical) research desks in hospitals. Nonetheless, each department currently can only have its one desk and the main focus remains on the contractual part, with less focus on collaboration with the laboratory and pharmacy. However, if these desks are set-up as a multidisciplinary platform for research, administration and organization, the clinical research process in hospitals becomes more efficient and it could provide a better facilitation for sponsors and CROs that perform clinical trials in the Netherlands.

Parties believe it would be preferential to set-up the research desks in such a way that these facilities are available for the departments, whilst at the same time they are not obliged to conduct the trial with the help of the research desk. Making use of the clinical research desk compulsory would only add another level of bureaucracy to the process. Additionally, successful investigators and their department will be discouraged from involvement if they have to share their achievement with the less successful departments.

Investments CRO and pharmaceutical industry

CRO and pharmaceutical industry are making efforts to improve collaboration with hospitals and hospital boards to overcome the collaboration bottlenecks (e.g. Quintiles' prime site and partner sites initiative and sanofi-aventis' Research Proof).

1.10 Recruitment of study subjects

Small patient pool

For therapeutic confirmatory trials, industry is nowadays looking at actual patient recruitment rates. The Netherlands, being a small country with a relatively small patient population, is not very competitive in this respect. CCMO data shows that approximately 100.000 patients per year are recruited for clinical trials, which is a relatively high number of patients for such a small country.

Reason participation

The most important reason behind a patients' decision to participate in a trial is their trust in the opinion of their treating physician. Other relevant factors that influence a patients' decision are the perceived image of the pharmaceutical industry and clinical research in general, and a lack of awareness of the benefits that can be gained from participating and in the subsequent improvement of healthcare. Nefarma is making an effort to remedy this situation.

Improve recruitment

Pharmaceutical companies and CROs are investing in the support and motivation of the investigational sites. They also emphasize the importance of a thorough feasibility assessment before opening a site. In hospitals it is important that everyone is aware of ongoing clinical trials, in order not to miss any potential subjects that visit the hospital.

Networks

The Netherlands has a solid infrastructure and excellent networks for gynaecology, cardiology, diabetes and hypertension at its disposal.

Healthy volunteers

The recruitment of healthy volunteers is not too problematic. The reimbursement is considered attractive, and advertising has proven to be very effective.

1.11 Collaboration industry, CROs and academic hospitals

In the Netherlands there are many collaborations between industry, government and academic hospitals. CTMM (Centre for Translational Molecular Medicine) and TIPharma (Top Institute Pharma) are public-private partnerships between government, industry and universities. These initiatives depend on input from local R&D, which now is only comprised of Organon (MSD). Unfavourable Intellectual Property arrangements make it difficult for local pharmaceutical offices to get approval for participation in these partnerships from the head office. Hospitals are also collaborating successfully on clinical trials at a national and regional level. These features can be further explored and manipulated in order to strengthen the position of the Dutch clinical research environment. Potential collaborations at a European level could be investigated, but realistically the Netherlands would then have to compete with other countries and different governments would interfere.

1.12 Access to well-trained CRO staff

Competitive market

The market for finding adequate, qualified and trained CRO staff is very competitive in the Netherlands. High salaries, good secondary labour conditions and fierce competition make it challenging. In addition it is not a prestigious industry to work in, which makes the pool of available staff considerably smaller. Where it used to be possible to hire several CRAs from a small local CRO, this is now much harder due to the large number of mergers and acquisitions in the CRO industry. In this way, the once small and local CRO has become a direct competitor.

The Netherlands as CRO country

Local pharmaceutical and biotech companies are not directly involved with respect to the availability of qualified local CRO staff for Phase II-IV studies. Decisions on contracting a CRO for these clinical trials are made at an international level and the CROs that are contracted are global organizations. It is therefore not worthwhile seeking possibilities to market the Netherlands as a good CRO country. Only in countries where the clinical research infrastructure and level of quality are not yet well developed is the choice of a local CRO critical.

1.13 The value of Dutch organizations

Value

All parties agree that the existence of organizations that are dedicated to the improvement of the local clinical trial climate, such as Nefarma, ACRON and DCTF, are very valuable. A successful initiative by the DCTF was to bring the hospital boards and industry players together in order to create a better awareness and understanding between parties. This in turn facilitates their collaboration and also improves the clinical research process. Life Sciences and Health is an organization that has built some useful bridges, but has not included the CRO industry thus far. In general, the opinion is that organizations are starting to make a positive difference to the clinical research environment in the Netherlands, but still have to increase their efforts in order to improve the Dutch competitive position in Europe and the rest of the world.

Influence

Nefarma has put great effort into establishing a good connection with the government and the CCMO. The ACRON and DCTF should aim to achieve a stronger say at a more structural level with the interested parties, including: government, the CCMO and the other authorities that decide upon the clinical research process and environment. Due to the importance of preventing further harmonization of the approval process and in doing so maintaining the Dutch competitive position for Phase I trials in the world, it is paramount that the ACRON and DCTF are able to convince the CCMO to take a stand on this topic. The impression is however that the CCMO does not acknowledge the ACRON and DCTF as valuable discussion partners yet.

Collaboration

The existing problems affecting the clinical research environment are often not approached in an coordinated way by the different organizations involved. Instead of joining forces, they are focusing on certain topics separately and in an isolated way.

1.14 Trends in clinical research

Shift to early phases

Several interviewed parties believe that, in the future the emphasis in clinical research will shift more towards the early stage trials. Because of cost saving, the industry is concerned with receiving more insurance on the potential failures and success of a product at an earlier stage. Expectations are that human testing will also start at an earlier stage. The Netherlands is well-equipped for the early stage research required for this type of testing (e.g. translational medicine).

Indications and compounds

In the past cardiovascular trials were very popular, but gradually a shift towards oncology trials became visible. The Netherlands enjoys a strong position in this respect, due to the large number of Key Opinion Leaders and good infrastructure in place for this indication. Other trends in clinical research are trials with small indications (development of specific innovative drugs), ageing diseases and paediatric trials. In the Netherlands there exist excellent networks for paediatric trials. A weakness exists here in that the regulations in the Netherlands (regarding this type of trial) are stricter than in other European countries and that the network has not yet able to mature. This makes pharmaceutical companies cautious when deciding in which country to base a paediatric trial. Personalized medicine (medicines developed for genetic subsets) and antibiotics research (because of the resistance that is developed for existing antibiotics) are also trends that can be expected in clinical research.

International collaboration

In order to maintain a meaningful position in the international clinical trial environment, it is important to focus on international collaboration. In the future, institutes may arise that focus more on hospitals than on countries.

Insourcing

Current expectations are that the industry is increasing the insourcing of knowledge, especially with regards to phase I research.

Publication of negative findings

The international development whereby negative and positive findings are both published is fully supported by academic hospitals. The industry agrees with this principle, but fears that the information is not always used for the right purpose.

1.15 The effects of globalization

Shift to the emerging economies

Now that pharmaceutical companies are looking at clinical research on a global scale, less expensive alternatives to the Western countries trials are appearing which can deliver results from a large amount of naïve patients. For therapeutic confirmatory trials (delivering patients and collecting data) there is a clear shift visible towards these countries, and it is impossible for the Netherlands to compete on this front. Furthermore, when industry links their investments in clinical research to potential revenues the Netherlands is not a very appealing country, due to the relatively small patient population.

The Netherlands is an interesting and exciting environment for more complex technical research, because of its good infrastructure, expertise and knowledge. The investigators in the emerging markets are very eager to learn and are developing at a fast pace, which in the long term will affect the Dutch competitive position in this research stage as well. At this stage it remains more expensive to manage clinical research in the more developing countries and cultural differences continue to provide hurdles to overcome, but it is only a matter of time. Further development will eventually bring these costs down to the level of Western countries. Therefore it can be concluded that the biggest driving force behind the shift to the emerging markets is and will be the recruitment of large numbers of naïve patients.

Acquisition of local R&D companies

To survive in a globalizing market, the industry has shown a trend in the past of companies acquiring or merging with other companies. For the Netherlands this means that international organizations are taking over local Dutch companies. Scientifically interesting research moves away to the head office or other core locations of these organizations.

The risk is that high-quality investigators and talented scientists are moving away from the Netherlands in order to work in locations where they can participate in scientifically interesting research with high quality facilities. This would be an undesirable situation, since the expertise and quality of our investigators are the pillars of Dutch clinical research. This would also mean that whilst investments are being made in the education of scientists, the Dutch clinical trial environment would not be able to benefit.

1.16 The role of the Dutch government

Organon (MSD)

Some of the interviewees were convinced that there was little the Dutch government could have done to prevent the acquisition of Organon and the subsequent decision to (possibly) close down the Dutch R&D unit. They are convinced that it is difficult to influence globalization

trends and the effect of market forces with which a multinational pharmaceutical organization has to deal with.

Others interviewed indicated their belief that the government should have acted more proactively instead of reactively in this situation, especially since MSD's decision directly influences the state of our knowledge economy and clinical research environment. The government should have communicated with AKZO-NOBEL at a much earlier stage, made a careful assessment of what the consequences of Organon's acquisition would be and also examined what possible options existed to influence that decision. Some also feel it would have made a difference, if at the time, prime-minister Balkenende had contacted the CEO of MSD to influence his decision (like Sarkozy supposedly has done) and fight for what is important for the Netherlands knowledge economy, instead of letting the market forces have a free hand.

Image

Several Dutch politicians are not very supportive of the pharmaceutical industry in the media. Instead of focusing on a few negative topics related to the industry it would be more appropriate to give credit to the industry for their involvement in the improvement of health care. Politicians should appeal to the people by stating that it is everyone's responsibility to support, collaborate and participate in the improvement process of our standard of care.

Collaboration VWS and EZ

The government should link economic activity to the clinical research and healthcare sectors in our country, with Finland providing an example of how to do so. The government should pay attention to investments made by pharmaceutical companies in the Netherlands and the possibilities that the government has to collaborate, motivate and support the industry, all of course within the boundaries of what is ethically justified. This would make the Netherlands a more attractive, efficient and productive country and will be beneficial to the status of a knowledge economy. To achieve this it is important for the departments of VWS and EZ to improve their collaboration and define common goals.

Long term vision

In order to build and expand our knowledge economy, the government should show a commitment to a long term vision and sustained continuity. TIPharma is for instance a very good initiative, but the short reigning terms affecting the government prevent the initiative growing and benefiting from previously offered investments. An alternative to this type of initiative is to start up research with governmental funding and subsequently search for external sponsoring in order to safeguard the continuity of the project.

Regulating responsibility

The government could support the clinical research environment by establishing clear and strict rules on timelines for local feasibility assessments. In other ways, it would help the clinical research environment if those regulations that account for unnecessary administrative burdens or regulations that put the Netherlands in a less competitive position are revised. These include the strict interpretation of the EU CTD with respect to gene therapy, orphan diseases and paediatric trials. In order to improve the quality of clinical research in the Netherlands, more governmental inspections could be carried out. However, this should not only be based on following strict regulations, but in accordance with the rationale behind the regulations.

1.17 Is the Netherlands an attractive country to establish your company

Company taxes

The Dutch tax regulations are very favourable and attractive for companies.

Rigid labour law

Labour law in the Netherlands is extremely rigid and in balanced favour of employees, which is a disturbing concept for a foreign company to consider when deciding whether to house their organization in the Netherlands. The fact that the decision concerning the reorganization of Organon (MSD) was postponed due to the privileges of the enterprise committee under Dutch labour law was not a good advertisement for the Netherlands as a country in which to establish a local office.

Negative image pharmaceutical industry

The image of the pharmaceutical industry in the Netherlands is worse than anywhere else in the world, due to the position of some politicians and academics that have access to the media. There is not enough understanding, awareness and appreciation of the positive aspects of sponsor initiated clinical research from which everybody benefits, such as improvement of our standard of care.

Input government

If the government wishes to make the Netherlands a more attractive country for the biotech and pharmaceutical industry it should link economic activities with scientific and healthcare activities. In addition, it would make the Netherlands a more attractive country if the government provided incentives to industry in order to stimulate clinical research in the Netherlands (e.g. like the government in Switzerland).

Reimbursement and prescription of compounds

After the long and extremely expensive process of developing a new compound, pharmaceutical and biotech companies have to overcome certain additional hurdles in order to make the development of the compound worthwhile. Their compound has to be added to the list of medicines that will be reimbursed by health care insurers otherwise their compound will not be prescribed by physicians. Pharmaceutical and biotech companies struggle to get their compounds on the reimbursement list in the Netherlands and in addition, Dutch GPs are very reluctant to prescribe new compounds, which is blocking further innovation and is discouraging for industry members.

2 SWOT analysis

2.1 Strengths

CA and METC approval process

- The CA approval process in the Netherlands is faster and more efficient than in other countries
- Timelines of the METC approval process for Phase I trials in the Netherlands are short compared to other countries, which is an important factor determining the current competitive position of Dutch Phase I clinical research

Infrastructure

- The Netherlands has an excellent Phase I setting
- Infrastructure for phase IV trials is very good
- Access to high quality investigators and research staff
- Access to technical knowledge, experience and expertise
- Excellent networks for gynaecology, cardiology, diabetes and hypertension
- Very good knowledge and information infrastructure with data from population compared to other countries in the world, and therefore very appealing for access and collection of valuable research information (e.g. clinicalresearch.com, iGuard, Provenance)
- Many collaborations between hospitals at a national and regional level
- Valuable interactions between universities and industry
- High standard of care

Training and education

- High educational level of investigators and research staff

Quality

- Availability of numerous important key opinion leaders
- High publication output for a relatively small country
- Good link between pre-clinical and clinical research
- Good at early stage complex trials
- Cultural tendency to collaborate internationally
- Well-equipped to handle more technical studies
- Image of reliable and incorruptible research environment

Business considerations

- Favourable company tax regulations

2.2 Weaknesses

CA and METC approval process

- A slow METC approval process for phase II and III trials, which makes the Netherlands an unattractive country for industry to select for their clinical trials, due to the eventual low patient recruitment. The Dutch neighbour country Belgium is performing substantially better in this respect.

Regulations

- Unnecessary administrative burdens when performing a clinical trial
- Lack of differentiation in regulations for different types of research

Infrastructure

- Limited motivation for investigators to participate in generic trials (financially and scientifically uninteresting)
- Small patient population available and not many treatment-naïve patients available. This makes the Netherlands not a very good “production country”.
- Hospital boards have a very negative perception of sponsor initiated clinical research

Training and education

- Insufficient classes on clinical trial topics (especially ICH-GCP) in the current curricula of relevant Masters degrees
- No central registration of investigators with an ICH-GCP certificate from an accredited institute
- No system for accredited ICH-GCP training and assigning accredited institutes

Business considerations

- Rigid labour law
- Image of industry in the Netherlands is worse than anywhere else in the world, due to statements by some politicians and the media
- Difficult to get on the reimbursement list of the health care insurers with a new compound
- GPs are reluctant to prescribe new compounds
- On a global scale, Western-European countries like the Netherlands are extremely expensive

Government

- No long-term vision and continuity by government of knowledge economy
- Insufficient collaboration between the departments of VWS and EZ: the government should aim to better link economic, scientific and health care activities

2.3 Opportunities

CA and METC approval process

- Assist investigators with the preparation and collection of submission packages for METC approval and local feasibility assessment
- Further professionalize management at the CCMO, in order to improve the clinical research process in the Netherlands

Regulations

- Adjust the requirements for trials involving orphan disease, paediatrics and gene therapy to mirror those in other EU countries (but no stricter) so that the Dutch clinical research environment can benefit from both the excellent networks in place and the status of these studies as pre-eminently interesting for its more unique technical knowledge and experience

Infrastructure

- Further develop the trend of establishing research desks in hospitals to facilitate the clinical trial process for industry and CROs.
- Create initiatives to improve the clinical research structure at hospitals and create awareness on hospital boards
- Improve patient awareness of the benefits of participating in a clinical trial
- Link patient data at a national scale in order to have access to a larger patient population.
- Further collaboration of hospitals on a national or regional level in order to have access to higher patient populations
- Improve awareness throughout hospitals of ongoing clinical trials in order to minimize possibility of missing out on any potential study subjects
- Maintain and further improve the excellent position of Dutch clinical research (infrastructure and high quality investigators) with respect to the more complex, early stage trials, that need scientific and technical input, since several expected trends in clinical research require this type of service (oncology, trials with small indications) (development of specific innovative drugs) (personalized medicine, translational medicine etc.)
- Make use of the excellent existing network (MRCN) in place for paediatric trials
- Maintain the Netherlands' strong position with respect to the wide availability of key opinion leaders
- Strengthen the position of organizations like ACRON and DCTF towards government, CCMO and other authorities, in order to influence decisions and to implement improvements for the clinical research environment
- Maintain the Netherlands' excellent position and setting for Phase I trials (expectations are that more Phase I knowledge is insourced)

- Stimulate collaboration between different players in research. The Dutch Medicines Days organized by the “Federatie Innovatief Geneesmiddelen Onderzoek Nederland” (FIGON) is an important initiative in this respect.

Training and education

- Arrange central registration and the obligation to pursue training at an accredited institute that provides appropriate (e-learning) training in ICH-GCP and create a system for assigning accredited institutes
- The success of the BROK-course is an opportunity to market the increase in the quality of the Dutch clinical trial environment to other countries
- Further improvement of ICH-GCP training and compliance

Business considerations

- Improved collaboration between the departments of VWS and EZ to make the Netherlands a more attractive country for investment
- Create incentives for parties that are useful to the Dutch clinical research environment

Government

- Nurture a knowledge economy principle

2.4 Threats

METC approval process

- Although it might be difficult to remain competitive on a global scale for certain types of trials (see below), at a European level it is still important to maintain and improve our competitive position. The slow METC approval process may result in the situation that pharmaceutical companies will move to other European countries where there is faster patient recruitment due to a more efficient METC approval process (signs of this development are already visible: Belgium is performing much better in this respect)
- Further harmonization of the METC approval process would immediately jeopardize the competitive position for Phase I trials in the Netherlands, since this would entail the levelling out of timelines at a European level. With the Phase I unit of PRA as the largest employer in clinical research in the Netherlands, this is a direct and serious threat to our clinical research environment
- The further harmonization of the METC approval will make for additional layers of delay

Regulations

- The stringent regulations regarding gene therapy and paediatric studies are a missed opportunity, since Dutch investigators and infrastructure is, well-equipped to handle these highly scientific studies. Currently, the most interesting studies in this scientific area are conducted in other European countries.

Infrastructure

- The lack of interest by specialists of participating in phase IIa studies will eventually lead to a situation where this type of research will disappear
- The absence of a research friendly mind-set in our key opinion leaders is a threat: in such a global environment where specialists in other countries are increasing their knowledge and reputation there is a possibility that this might lead to a shift to countries where key opinion leaders are well-equipped and eager to participate at the operational level of the trial

Emerging markets

- Sponsors are increasingly basing their decisions upon where to conduct their clinical trial on hard and actual figures regarding patient recruitment and the potential future market. For less complicated confirmatory studies the research environment is also available in less expensive countries, where the sponsor has access to a large naïve patient population. Due the limited size of the patient population (determined by the size of the country and high standard of care) and the small potential future market it is impossible for the Netherlands to compete with these countries on this type of trials
- There is a risk that the Dutch clinical trial environment may underestimate the speed of development in emerging markets. It is crucial to further develop the strengths of the Dutch clinical trial environment, in order to remain competitive

Globalization

- Departure of the R&D activities of industry will lead to loss of collaboration on joint ventures between industry and academic hospitals
- Due to the departure of the local R&D units of large pharmaceutical companies, it is likely that talented investigators are leaving the country. Since the quality of these investigators is one of the current environments' biggest strengths (and if disregarded would amount to a loss of investment in education) it is crucial to sustain the position of the Netherlands as an appealing location in which to perform scientifically interesting clinical research.

3 Recommendations

In addition to the recommendations made in the “Opportunities” section above, please find below a summary and completion of the recommendations for the improvement of the clinical research climate in the Netherlands. This section will provide recommendations that can be used as a starting point for further assessment at a more detailed level on how to approach and implement the required improvements.

METC approval process

- Make all required efforts to maintain the Netherlands’ competitive position for Phase I trials on the global stage. This means that the ACRO and DCTF have to make a serious and concerted effort to strengthen their position in relation to organizations that can influence this decision, such as the CCMO and EMA and make a solid, united stand in regards to this topic
- Improve the METC approval process, by implementing clear timelines for the local feasibility committees (with Belgium as an example), invest time in collaboration with hospital boards, support investigators with the preparation of the submission package and further support and stimulate the national committee that streamlines the process for METC approvals

Regulations

- In order to avoid a disproportionate administrative burden and discourage investigators, it is recommended that there is an attempt made to differentiate in the regulations for clinical research (for investigators and pharmacies) between (smaller) investigator initiated trials and (large) industry sponsored trials
- The implementation of the EU CTD has increased bureaucracy in all EU countries. It would however be beneficial for the competitive position of the Netherlands to assess whether there are administrative processes and regulations that can be adjusted in such a way that bureaucracy will decrease (while respecting EU guidelines) and the Netherlands can become a more attractive country for clinical research
- Adjust requirements for trials involving orphan diseases, paediatrics and gene therapy to those requirements in other EU countries (but not stricter) so that the Dutch clinical research environment can benefit from the fact that they are very well equipped for this type of study

Infrastructure

- Hospital should receive incentives from government and industry to support the establishment of research desks

- Create initiatives that can improve the clinical research structure at hospitals and create awareness on hospital boards
- Improve the general perception of industry sponsored trials within hospitals, so that it becomes more interesting for investigators to participate
- Take advantage of and embrace the development that, the emphasis will shift to the earlier phases of clinical research for cost efficiency reasons, sell our expertise on translational medicine, predict pharmacodynamic effects and other early phase research, because this is one of the Netherlands' biggest strengths
- Further strengthen the Dutch MCRN network and draw international attention to this network in order to increase the number of paediatric trials in the Netherlands which contribute to increased experience
- Create opportunities for interesting scientific research in the Netherlands and attract R&D from industry in order to hold on to the Dutch key opinion leaders
- Make an effort to improve the research-unfriendly mind-set of many key opinion leaders in order to remain competitive with countries that are developing fast and will be able to provide alternative knowledge and expertise. On top of that, a research-friendly mind-set should be developed in order to remain attractive for the industry
- Stimulate further collaboration between industry and academic hospitals

Patient access

- Link patient data nation-wide and promote and develop collaboration and networks in order to have access to a larger patient population
- Strengthen and improve existing patient networks in the Netherlands and make use of existing patient organizations
- Encourage awareness at hospitals of ongoing clinical trials in order to not miss out on any potential research participants
- Increase patient awareness of the benefits of participating in a clinical trial
- Invest in relationships with GPs in order to facilitate patient access for GP indications

Training and education

- Encourage universities to incorporate classes on clinical trial topics (especially ICH-GCP) in the curriculums of relevant Masters degrees
- Assign accredited institutes that can provide ICH-GCP training by way of e-learning and centralize the registration of training certificates
- Further support initiatives that improve ICH-GCP compliance and awareness of the Dutch investigators

- Use the current and ongoing improvement of ICH-GCP training and compliance (e.g. BROK-course) to market the quality of Dutch clinical research to other countries

Organizations

- The organizations in the Netherlands that are working on the improvement of the Dutch clinical trial environment (Nefarma, DCTF, ACRON and Life Sciences and Health) should, wherever possible, join forces in order to effectively identify existing problems and find solutions in an coordinated manner and to effectively implement improvements (as an example see for instance the “The Initiative” in Belgium: www.theinitiative.be)
- DCTF and ACRON should create a stronger position in relation to the CCMO, government and other authorities at a local or international level in order to exert more influence on decisions that directly affect the state of the clinical trial industry in the Netherlands

Business considerations

- Improve collaboration between the departments of VWS and EZ in order to link economic activities with scientific and healthcare activities. Furthermore, the government should try to create interesting opportunities for the industry (and thus for the Dutch research environment)
- Provide financial incentives to industry in order to strengthen the Dutch clinical trial environment

Government

- The Netherlands should differentiate itself from other countries by offering a high level of infrastructure and services with support from the government, with Switzerland as an example
- The government should create a long term vision for establishing and stimulating our knowledge economy
- The government should carry out more inspections in order to increase the quality level of clinical research in the Netherlands. However, this should be done in accordance with the rationale behind the regulations and not simply by stringently following strict regulations
- The government should make an effort to improve the image of the clinical trial industry by creating a better understanding, awareness and appreciation of the positive aspects of sponsor initiated clinical research, from which everybody benefits (such as improvement of our standard of care)

Globalization

- Create improved collaboration with other EU countries and together strengthen the position of Europe as a clinical trial region. It is better to look for international

collaboration and let other countries learn from our specific strengths than to strengthen our position as a single country

- Improve international collaboration in order to maintain a participating position as a smaller country in the clinical research environment

SECTION 2: INTERVIEWS

T. van Gelder, MD (Erasmus MC, Rotterdam)

27 August 2010, Rotterdam

Name: Teun van Gelder, MD

Organization: Erasmus Medical Centre, Rotterdam

Title: Internist - nephrologist and clinical pharmacologist

Description of the Organization: The Erasmus MC is the largest of the eight university medical centres in the Netherlands. The core activities of the Erasmus MC are patient healthcare, research and education. Scientific research has become one of the most important activities of the Erasmus MC. Currently, the Erasmus MC is ranked as one of the forty best research institutes in the World.

Professional background and role in organization: Since 1988, Teun van Gelder has worked as an Internist - nephrologist and clinical-pharmacologist at the Erasmus MC and has been involved in clinical research since 1990. Since august 2010 he has been working as a Professor in Clinical Pharmacology at Erasmus MC. Teun van Gelder is Vice-Chairman of the METC of the Erasmus MC (6 years), and chairman of the BROK-course¹ committee.

METC approval process

The general perception in the Netherlands is that the METC approval process is slow. However the situation is comparable in other countries. A substantial development to improve the process has recently occurred: whereas in the past all hospitals participating in a clinical trial wanted to make their own assessment, nowadays one METC is making the assessment and the other hospitals only make an assessment on the local feasibility assessment and patient information. A national committee has been established to further streamline this process. The national committee helps by assisting investigators to develop a good quality of informed patients willing to consent and by attempting to facilitate the collaboration of the METCs. At the Erasmus MC, the local feasibility assessment is not carried out by the METC anymore, but by an independent committee. This process has facilitated the METC process tremendously.

The time required to receive METC approval could be further improved, but obtaining the METC approval is often not the time consuming factor (although it is usually presented that way). We should, also look at the time taken between the METC approval and the first patient being enrolled in the trial, which is sometimes very long (often six months or more). This delay

¹ [Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers](#) (BROK)

is often due to the investigator (too busy, no motivation), or alternatively the sponsor or CRO can be guilty of delaying the process.

A central European METC is at this stage not desirable. It will be difficult for METCs in the Netherlands to accept the assessment of METCs in countries with less experience in clinical research and it will further delay the process.

Effects implementation EU CTD

The regulations in the Netherlands were already adequate before the implementation of the EU CTD. The implementation of the 60-day timeline for the METC approval process is an improvement. A better compliance with ICH-GCP is visible, which is the result of further professionalization of the research environment stimulated by the EU CTD. However, the implementation also created a lot of administrative burden. It is not always clear how patient safety benefits from this.

The extensive reporting requirements make it more difficult for an investigator or an METC to keep a good overview, and derive the relevant information. Data safety monitoring boards are better equipped to control the many reports and make the right assessments. This is beneficial as the investigator and METC can rely on them. At the EFGCP (European Forum for Good Clinical Practice) meeting in Brussels there was a possibility to discuss these topics. Unfortunately, the attendees consisted mostly of regulators and not investigators, leading to insufficient emphasis on discussions to reduce bureaucracy. Of note, the report of the European Science Foundation is very helpful². It provides good recommendations for reducing bureaucracy, for instance by differentiating between low-risk and high-risk research.

Data Protection

The effects of the Data Protection Directive are not yet visible. Certain data protection issues that the hospital have to deal with, can include requests from the sponsor of a clinical trial who wishes to have access to the source data, and even wishes to receive copies of the patient files, which is of course not acceptable.

Negotiating site agreements

Contract negotiations tend to be slow as the contracts submitted to the legal department of the hospital often are based under foreign law, and may require changes related to the local situation. Sometimes delays are also caused by unreasonable demands of the sponsors. Often the agreements are submitted at the end of the METC approval process.

² European Science Foundation (2009) – Forward Look - Investigator-Driven Clinical Trials

A standard clinical trial agreement as proposed by the CCMO will only result in time reduction if the template is supported by a substantial platform of all parties involved in clinical research in the Netherlands (local subsidiaries of the pharmaceutical companies, the CROs and the academic hospitals), similar to the UK approach. A standard template that is created unilaterally will not be accepted by all parties involved and will not reduce the negotiation time.

The quality of clinical research in the Netherlands

The Netherlands is known internationally for its high quality education and its scientifically well trained and high quality investigators. There is industry consensus in the strengths of the Netherlands: reliable data, timely reporting, minimal fraud etc. In addition, in the Netherlands there is good communication between the pre-clinical and clinical part of research. It is important for pre-clinical and clinical researchers to be able to have thorough discussions on their collaboration and transition of the research phase.

Recruitment and motivation of investigators

Sponsor initiated later phase clinical research is not always very interesting for an investigator. Especially as the bigger pharmaceutical companies have in-house expertise and do not ask for a lot of input from the investigators. Sometimes (smaller) pharmaceutical companies ask for some input through advisory boards or special interest groups. The pharmaceutical companies are often less interested in the pre-clinical part of the study. In order to make conducting trials appealing to investigators, in the Erasmus MC the investigators often negotiate the possibility to also set up sub-studies (and ask for sponsoring) that create a link with the pre-clinical phase. This enables them to obtain answers to questions that are interesting to the investigators. Investigators can often not participate in the publications of sponsor initiated multi-centre trials: in many cases only e.g. the top 10 recruiters will receive this privilege. Financially it is also not very interesting: a reasonable reimbursement is provided for the services, but with the increased regulations a lot of resources are needed (research nurse etc.).

In general, Dutch investigators are still enthusiastic to participate in clinical trials, and want to participate in the world-arena. There can be big differences between the different departments: some departments are very active in clinical research and have a good link with industry, whereas other departments are not interested (it is often “a matter of tradition” within the department). Financially there is no conflict of interest since the remuneration always goes to the relevant department of the hospital and not directly to the investigator.

Training and education investigators

Erasmus MC is paying a lot of attention to ensure proper opportunities for training people to become a liaison between basic clinical research and the lab, for example by offering a Master's degree to its students where they are trained in this task. The University of Groningen is offering the GUIDE course ("Good Research Practices: GCP and GLP) in which they combine the pre-clinical and the clinical phase in research (see above). The BROK course plays an important role in ensuring that investigators are trained in and operate in compliance with ICH-GCP guidelines.

As the chairman of the BROK-course committee, Teun van Gelder is planning to write an editorial in the British Medical Journal of Medicine or Clinical Pharmacology and Therapeutics in order to present evidence that Dutch clinical research has improved in quality because of this initiative. Investigators from the STZ (Association of Teaching Hospitals) hospitals are also interested in the course, and can join at the academic hospitals in their area. Unfortunately, in some of the UMCs, the demand for the course is often higher than the supply.

Infrastructure hospitals

Industry sponsored studies are not supported from within the hospitals, The prestige of industry sponsored studies is less than studies funded by governmental organizations like ZonMw and NWO (e.g. Veni, Vidi and Vici beurs). The greater difficulty in obtaining funding, the higher the prestige. The hospital board does not offer finance support for industry sponsored clinical research. If the investigator wishes to participate, he has to negotiate with the sponsor for the reimbursement for the costs and required resources.

A central clinical trial desk that facilitates support for clinical research is a good idea, but in practice will be difficult to achieve. The more successful departments do not wish to share the results of their success and their infrastructure with the less successful departments. In the Erasmus MC, the department that is most successful will get the largest part of the remuneration. In Maastricht they have established a central clinical trial desk that is funded by the investigators: the CTCM (Clinical Trial Centre Maastricht). As expected not all investigators are enthusiastic about this initiative.

Recruitment of study subjects

The Netherlands is a relatively small country, with consequently not a very large patient population. Since initiating a clinical trial in an additional country is very costly, the industry often chooses to initiate the studies in foreign countries where more patients are available. Local R&D units of the industry often "fight" for their country, so that their office is not ignored.

Clinical trials in the Netherlands often perform relatively well in respect of the recruitment of patients. Patients are eager to participate, since they have a lot of confidence in their treatment by physicians. In order to prepare potential study subjects for the possibility of participating in a trial, the investigators have good contacts with the patient organizations.

Trends in clinical research

Teun van Gelder totally supports the international development that negative findings need to be published as well as the positive findings (See e.g. FDA Amendments Act 801). In the Netherlands Journal of Medicine he has written an editorial on “the importance of reporting negative findings”³, in which he emphasizes that negative findings are also scientifically important. Teun van Gelder also advocates that editors of scientific magazines encourage investigators to divulge that a case study is cancelled for safety reasons.

The effects of globalization

It is likely that with the departure of R&D units like the one from Organon (MSD) to their head offices, promising scientists and investigators will move to the countries where the industry performs scientifically interesting research. Some investigators prefer to work in an academic hospital, because they have more freedom in the choice of the research area (and in such a case they are not very likely to move abroad). On the contrary, for some investigators it is also very attractive to work for a pharmaceutical company, since they offer high quality research facilities and as an investigator you do not have to find external funding.

The role of the Dutch government

It is remarkable that the government did not prevent the acquisition of Organon at the time, and that they did not try to invest in order to save the R&D unit for the Netherlands. Investing in Organon instead of selling it would have been more in line with the principle of the knowledge economy and the investments in clinical research already made. The current developments at Organon (MSD) are not a big surprise. It is however, difficult to judge if the government really could have did more, since the interests and objectives of a big company and the government will always be different.

³ T. van Gelder (2007). The ups and downs of sirolimus in kidney transplantation, and the importance of reporting negative findings. The Netherlands Journal of Medicine, volume 65 (no. 1), page 7-8.

SWOT Analysis

<p>Strengths</p> <ul style="list-style-type: none"> • Improved METC approval process • High quality education and investigators • Good clinical research image (“reliable”) • Good link between pre-clinical and clinical research 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Administrative barriers involved with performing a clinical trial • Sponsor-initiated trials are often not scientifically and financially interesting enough for investigators, they do also not get enough prestige • We do have a relatively small patient population
<p>Opportunities</p> <ul style="list-style-type: none"> • The BROK course is an opportunity to sell the improved research quality of the Netherlands abroad • Nurture the knowledge economy principle 	<p>Threats</p> <ul style="list-style-type: none"> • Talented scientists will move abroad to follow the more interesting R&D activities of the industry

Recommendations

- Make industry sponsored trials better respected and appreciated within the hospitals, so that it becomes more interesting for investigators to participate
- Use current Dutch initiatives with respect to ICH-GCP compliance (e.g. BROK-course) to sell the quality of the Dutch clinical research abroad

P.A.B.M. Smits, MD FFPM (Radboud University Nijmegen Medical Centre)

3 September 2010, Nijmegen

Name: Paul Smits, MD FFPM

Organization: Radboud University Nijmegen Medical Centre

Title: Head of the Department of Pharmacology and Toxicology

Internist and Professor of Pharmacology at the Radboud University Nijmegen Medical Centre (since 1995)

Scientific Director Research Institute 'Nijmegen Centre for Evidence Based Practice'

Chairman 'Instituut Waarborging Kwaliteit en Veiligheid' in Radboud University Nijmegen Medical Centre.

Description of the Organization: The Radboud University Nijmegen Medical Centre is an Academic Medical Centre that combines patient healthcare, education and research. The Radboud University Nijmegen Medical Centre is a top knowledge centre for academic medicine and health care, and as such also involved in clinical research.

Professional background and role in organization: Paul Smits is an internist at the Radboud University Nijmegen Medical Centre and in his function as head of the Pharmacology-Toxicology department, involved in clinical research. His expertise concerns cardiovascular research and is specifically focused on the stage during which the pre-clinical part of a trial is transposed to the clinical part ("proof of concept" studies). The studies in which he is involved are often small-scale investigator initiated studies with a placebo-controlled, randomized study design. However, he is also involved in later phase industry sponsored trials.

METC approval process

The METC approval process at the Radboud University Nijmegen Medical Centre is very well organized. Radboud University Nijmegen Medical Centre has its own Commission on Research Involving Human Subjects, and they are very efficient and perceptive for good arguments and as such are not a delaying factor in the process.

Effects implementation EU CTD

Implementation of the EU CTD has resulted in greater levels of bureaucracy for investigators. This is especially true given the fact that (smaller) investigator initiated trials are treated in a similar fashion to (large) industry sponsored trials with regard to the laws and regulations. This is a frustrating and discouraging factor. Greater differentiation in laws and regulations, between different types of clinical research would solve this situation. The same situation applies to pharmacies (GMP), which are bound by very strict rules of inspection. They are

required to have a very complex infrastructure, even in not particularly complex situations. It would be helpful if, in this case common sense prevails and a differentiation is made in order to avoid unnecessary delays.

An example here is a study initiated by Paul Smits 2,5 years ago which focused on an endogenous substance: it has not yet started, due to the extensive administrative and approval requirements. Obviously safety has to be taken into consideration, but common sense should also be applied. The risk is, that a lot of time is invested in a scientifically important idea, and eventually investigators in countries where less strict laws and regulations are in place will catch up. These countries will be able to finalize a clinical trial on the subject matter before the Netherlands do.

Negotiation of site agreements

In the past, the negotiations surrounding site agreements were not concluded in an efficient and timely manner. However, since the Radboud University Nijmegen Medical Centre opened a valorisation department with its own lawyers (possessing industry knowledge), this process has improved considerably and has become more professional (also with respect to patent protection etc.).

The quality of clinical research in the Netherlands

The Netherlands has a good reputation with respect to clinical research, due to high (scientific) investigator quality and the presence of many Key Opinion Leaders. The Netherlands is known for its high level of education and high quality universities. In addition, the Netherlands is perceived as a country that is down to earth and takes the reliability and integrity of the study data very seriously.

Costs

For the industry the Netherlands is an expensive country: the costs are relatively high due to the many layers of bureaucracy and the high salary level in the Netherlands.

Recruitment and motivation of investigators

Sponsor initiated trials are not very interesting if there is no possibility for scientific output or publication. The money earned with a clinical trial is not a motivating factor for an investigator: usually the workload is relatively high and the money comparatively low. Even in a multi-centre international setting, such a trial is unlikely to be scientifically interesting, unless an investigator participates as a Key Opinion Leader for a certain indication.

The industry is also sometimes interested in small-scale proof-of-concept studies: they can test a small patient population and get an indication of the outcome of a clinical trial, which can

save them money in the long term. This type of study is also often scientifically more interesting for an investigator.

Whether an investigator prefers to participate in a more technical study or a more applied clinical trial with certain endpoints, eventually depends on the specific interest and possibilities of the investigator concerned. Universities will generally prefer more ground-breaking research, whilst the larger hospitals are usually interested in applied clinical trials, as they do not have access to the required techniques and setting for proof-of-concept studies.

Training and education investigators

All investigators (doctoral students and their mentors) involved in clinical research at the Radboud University Nijmegen Medical Centre are obliged to participate in the BROK-course, in order to ensure solid knowledge of ICH-GCP guidelines. The training requirements for clinical drug research are perceived as disproportionate by the investigators compared to other types of research and therefore sometimes have a discouraging effect.

Infrastructure hospitals

In general, the internal support from hospitals for the performance of clinical trials is not substantial. At the Radboud University Nijmegen Medical Centre, effort is made to improve the situation through the establishment of the CRCN (Clinical Research Centre Nijmegen). CRCN's objective is to create a platform where a lot of expertise, facilities and support is provided for conducting a clinical trial. The costs for making use of the CRCN are met by the department concerned. The investigator has three choices when performing a clinical trial: a) arrange the trial individually, but ensure that it is performed in accordance with ICH-GCP (the hospital board will check compliance by way of internal audits), b) perform the trial completely with CRCN or c) perform the trial individually, and make use of CRCN expertise.

In addition, the Radboud University Nijmegen Medical Centre has a gratuity system that stimulates research on the basis of performance: if an investigator at the Radboud University Nijmegen Medical Centre has shown its (scientific) contribution to the hospital, by way of publications, mentoring promotions and arranging funding for the hospital, an investigator gets the possibility to become a Principal Investigator (PI) at the hospital. In such a case, the department will receive funding from the hospital in order to free up time for the PI to perform research and further professional development.

Recruitment of study subjects

The recruitment of patients for a clinical trial is often underestimated and are almost never in line with projections. Important factors are that, there exist extensive inclusion criteria

required by the protocol, and investigators are often fishing in the same patient pool. The recruitment of healthy volunteers is a lot less complicated, due to advertising and the interesting payments available for volunteers and also the fact that with this type of study the exclusion criteria are more significant.

The Radboud University Nijmegen Medical Centre owns a database containing patient data, therefore they can contact the doctors from the hospital to enquire if patients can be approached for a certain clinic trial. This is a development that can be further improved by better IT support and input. In this perspective "*Parelsnoer*" is worthwhile mentioning: an initiative between the academic hospitals to set-up a nation-wide bio-bank. This could also be achieved for patient data. The "*Interuniversitair Cardiologisch onderzoeksinstituut*" (ICIN) is a good example of how that could work: they collaborate nation-wide in order to have access to the required large number of patients for a clinical trial. The Radboud University Nijmegen Medical Centre has a department for first line medicine that has an excellent network for clinical research with general practitioners in the area of Nijmegen, which can be used as a source for study subjects.

The image of clinical research ("guinea pig" idea) when participating in an industry sponsored trial sometimes plays a role in patient decision making on participation. For investigator initiated trials and studies with healthy volunteers this plays a less significant role.

Collaboration industry, CROs and academic hospitals

The interaction between industry and universities is good. The Radboud University Nijmegen Medical Centre is in contact with Organon (MSD) at different levels. The Centre for Translational Molecular Medicine (CTMM) in Eindhoven and TI Pharma in Leiden are both joint ventures between the government, the industry and the universities. The government stimulates the collaboration between industry and universities. This initiative is dependent on the input of the R&D units from the industry, which is now only Organon (MSD). A next generation of government initiated projects are not very likely, now that the R&D unit of Organon (MSD) has closed down and been transferred to the United States. Maybe now we should explore opportunities at a European level. This will of course be more complicated if the Netherlands has to compete with other countries and face different governmental interference. Another option is to seek collaboration with the other UMCs and perform study prepare protocols and SOPs together etc. This could prove stimulating for centrally organized clinical research.

Trends in clinical research

The development of technologies with artificial organs (e.g. artificial kidney and liver) can generate important information at an early stage, so that it can be tested on human beings at a fairly early stage. Another trend in clinical research is personalized medicine: clinical research will be based more on polymorphism and specific patient features. There has been a shift in discussions on how a clinical trial should be arranged: e.g. whether responders and non-responders should be looked at separately and if kinetic polymorphisms should be included.

The effects of globalization

Because there are many options on a global scale, it has become less interesting for the industry to perform clinical trials in the Netherlands, because of the high costs (see above). It is only a matter of time before other countries will improve in quality and industry driven research will move abroad to more cost efficient countries.

For investigator initiated research, the situation is different as the knowledge and expertise required for this type of study is not so easily available in the emerging markets. The only danger is that because of excessive regulations this type of research is discouraged. The other important effect of globalization on the industry, is that with the departure of Dutch R&D units to head offices abroad, this leads to very serious negative impact on the clinical research environment in the Netherlands.

The role of the Dutch government

The fact that the appropriate governmental departments did not communicate with Hans Wijers on the importance of the knowledge economy and the effects that the acquisition of Organon by Schering Plough would have in that perspective, was a missed opportunity. We should be able to trust the government to make the right decisions in this type of important strategic situation, and now there is little they can do. The only opportunity available to save the R&D unit from Organon (MSD) is through acquisition by another large pharmaceutical company.

In general, the Dutch government could play a role in the improvement of the clinical research environment by down-grading the laws and regulations to an acceptable level, so that the Netherlands remain competitive. In addition, The Dutch inspection could be more active in order to increase the level of clinical research, provided that the inspections are done by the basic principles of clinical research and not marginal regulations.

SWOT Analysis

<p>Strengths</p> <ul style="list-style-type: none"> • Good image investigators • Many Key Opinion Leaders • Good universities • Reliability and integrity of the research climate • Valuable interaction universities and industry 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Bureaucracy • Lack of differentiation in regulations for different types of research
<p>Opportunities</p> <ul style="list-style-type: none"> • METC approval process is improved • ICH-GCP compliance investigators is improving (BROK-course) • Support from hospital is improving • Link patient data nation-wide and other nation -wide recruitment initiatives and networks in order to have access to a larger patient population • Personalized medicine • Shift to pre-clinical and early phase trials 	<p>Threats</p> <ul style="list-style-type: none"> • Cheaper countries also gradually provide good quality • Loss of expertise from the industry (Organon) • Loss of collaboration with the industry (Organon) • Investigators are not very interested in international trials • Patient recruitment underestimated

Recommendations

- Differentiate in the regulations for clinical research (investigators and pharmacies) between (smaller) investigator initiated trials and (large) industry sponsored trials
- Reduce regulations in order to become quicker and cheaper and therefore more competitive
- Link patient data nation-wide and create collaboration and networks in order to have access to a larger patient population
- More inspections by the government in order to increase the level of clinical research in the Netherlands

F.H. Bosch, MD (Rijnstate Hospital/Alysis Zorggroep)

6 September 2010, Arnhem

Name: Frank Bosch, MD

Organization: Rijnstate Hospital/Alysis Zorggroep

Title: Internist

Description of the Organization: The Rijnstate Hospital is part of the Alysis zorggroep and a member of the Association of Tertiary Medical Teaching Hospitals (STZ – samenwerkende topklinische ziekenhuizen). Besides the treatment of patients, Rijnstate Hospital focuses on applied clinical research and innovation in healthcare.

Professional background and role in organization: Frank Bosch has been working as an internist at the Rijnstate Hospital since 1989. Primarily, he is involved in investigator initiated research, which results in high standard publications once every 2 to 3 years. Occasionally he will also participate in sponsor initiated clinical trials, but only when there is an added scientific value. The clinical research performed in the hospital is principally Phase II to IV research. There is not a great deal of drug related research that directly correlates to the patient population for whom he is responsible (i.e. intensive care patients). Frank Bosch was previously manager of the “leerhuis” of the Rijnstate Hospital, the core objective of which is to facilitate education and development for the hospital and its staff. He is a board member of the DCTF and president of the Dutch Internists Society.

METC approval process

At the Rijnstate Hospital, the local approval process has been improved substantially. There is a regional METC and a separate local feasibility committee. The duration of the METC approval process is not usually the principal delaying factor. The time that elapses between approval and enrolment of the first patient in the study takes a substantial amount of time in the clinical trial process. However, this parameter is never measured or mentioned in this perspective. Implementing a European METC approval will only add additional administrative layers and thus increased bureaucracy.

Effects implementation EU CTD

There are no substantial changes visible since the implementation of the EU CTD. It is also currently difficult to determine how the implementation will eventually influence the Dutch clinical research environment, since the regulations have not yet been executed in all of its areas. The only evident change has been the increase in administrative burdens.

Standardization of clinical trial documents

Unambiguous and good quality patient informed consent forms will improve the conduct of clinical trials, since it will facilitate improved patient inclusion.

The quality of clinical research in the Netherlands

The Netherlands is a small country with a relatively high number of qualified individuals and organizations. The Netherlands has a significant number of useful collaborations in place and an excellent health care system. The Netherlands is performing very well in terms of clinical research, when considering the amount and level of research carried out and the number of high quality publications produced by Dutch investigators. The quality and education of the investigators and study nurses is excellent.

Costs

The costs of a clinical trial are not deemed as important by a sponsor as the opportunity to set up the right infrastructure and research process for their clinical trial.

Motivation of investigators

Payments made to an investigator by the industry, for clinical research, are reasonable in relation to the services provided (as required by ethical norms) but, are not the most important incentive for the participation of the investigator. The scientific value of a study is in that sense more decisive.

Training and education investigators

In the past it proved a challenge for the Rijnstate Hospital to track all the investigators that were trained on ICH-GCP. The hospital is now working on a proper registration system for the training of investigators and has implemented a “teach the teacher” program and an ICH-GCP course for their investigators.

Infrastructure hospitals

The conducting of clinical research trials is not supported by the hospital (financially or otherwise) but instead based on the individual decision of the investigator. The hospital board is not particularly positive about collaborating with the industry: the perception from the hospital’s viewpoint is that industry sponsored clinical research is costing the hospital a large amount of money and the specialist is the party that benefits financially. It often proves difficult holding the hospital responsible for costs incurred when treating a patient that is participating in a clinical trial. The question should be: do hospitals have an obligation to perform clinical research and if so, should they receive payment for providing this service?

Recruitment of study subjects

For successful patient recruitment, it is very important that every member of the relevant department (maybe even every member of staff at the hospital) is aware of the existing and ongoing trials. For the type of studies in which Frank Bosch is involved, recruitment of patients takes place at the intensive care unit. In his department, everybody has the same objective: all patients are assessed to determine if they are a viable potential participant for the study. Recruitment is, for instance, more complex for a hypertension trial at a polyclinic: usually not all doctors working at the polyclinic are involved in the relevant clinical trial and the completely different authorization structure for making the assessments can prove problematic. Prospective patients for the clinical trials at the Rijnstate Hospital are usually not recruited through referral by the first line of care.

The willingness to participate in a clinical trial depends on the study type (it is, for example, easier to recruit patients for comparative study of two registered compounds than for an antibiotics trial). The negative image of clinical drug research and a lack of awareness about the benefits of participating in a clinical trial, influence recruitment.

Collaboration industry, CROs and academic hospitals

In the Netherlands we have a strong position as regards clinical research, due to of our excellent networks. Both the cardiology and gynaecology networks are extremely good and hospitals are collaborating on clinical trials at a national and regional level. Examples are the dialysis research that is performed by the Rijnstate Hospital together with the VU, the collaboration of the Rijnstate Hospital and the Radboud University Nijmegen Medical Centre on different trials and the PROPATRIA-trial that was done with through the collaboration of 40 hospitals in the Netherlands. This is an important feature of the Dutch clinical trial landscape that could be further developed to strengthen its position. The collaboration between industry and universities is seriously impacted by the departure of the R&D unit of Organon (MSD). Many initiatives that were ongoing between Organon (MSD) and the universities will now disappear.

The value of Dutch organizations

The initiative to facilitate dialogue between the hospital boards and the pharmaceutical companies lead by the DCTF has proved successful. The hospital boards are often not exposed to the benefits of performing industry sponsored clinical trials and it would be of added value for the clinical research environment in the Netherlands if they collaborated with industry more effectively and often.

Trends in clinical research

A new development is that of tailor-made medicine: it involves pharmacogenetics and requires a high standard of technological environment, therefore proving interesting for countries in Western Europe. The central concept is that the genetic profiles of the study subjects are matched with the profiles of the patients who will subsequently have to use the medicine. The expectation is that the number of drug takers in the Netherlands will increase. It is important that we facilitate the right infrastructure that will be able to accommodate and stimulate such a development. Furthermore, the focus of clinical research in the near future will depend, to a large extent, upon the personal interests of the investigators.

The areas of attention that were determined by the Rijnstate Hospital last year were vascular care, oncology and immunology. The hospital also hopes to maintain its position as the number one hospital in Europe, in the field of bariatric surgery. In the future it is important to focus on international collaboration opportunities and to ensure the continuance and establishment of political ties with other countries. Research institutes might spring up in years to come that place a greater focus on hospitals than countries.

The effects of globalization

It might currently prove very appealing for industry to look towards cheaper alternatives in other countries. Such a shift of clinical research to the emerging markets will not be a long term development however: in 5 to 10 years the costs in these countries will have increased and the Netherlands will again be more competitive with respect to costs. Large scale cardiovascular intervention studies are migrating to countries that are able to process large numbers of patients within a short period of time.

The role of the Dutch government

The short reigned and limited powers of the Dutch government are resulting in a lack of continuity and a failure to take responsibility for decisions made in the clinical research and health care environment. The government is often unaware of the consequences of their decisions and lacks integrity in their approach (e.g. the decision to cut the salary of specialists was done at the same time as allegedly wanting to maintain the high level of health care).

The situation regarding Organon (MSD) is a difficult one for the Dutch government to solve. If the government wishes to invest in the R&D unit, the unit should be able to continuously provide added value for the clinical research environment in the Netherlands and should create even tighter connections with universities.

SWOT Analysis

<p>Strengths</p> <ul style="list-style-type: none"> • High number of qualified investigators • Excellent health care system • Excellent networks (e.g. cardiology and gynaecology) • Numerous collaborations between the hospitals at a national and regional level 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Hospital boards have a negative perception of sponsor initiated clinical research • Lack of continuity evident in initiatives from the government to stimulate the knowledge economy
<p>Opportunities</p> <ul style="list-style-type: none"> • Further improve ICH-HCP training and compliance of investigators • Improve collaboration between the industry and the hospitals • Improve awareness throughout hospitals of ongoing clinical trials, so that all patients visiting the hospital are “screened” on their potential participation • Improve awareness of benefits of participating in a clinical trial • In the long term the costs of the emerging markets will not be as competitive as they are now 	<p>Threats</p> <ul style="list-style-type: none"> • The closure of the last R&D unit from the industry in the Netherlands will jeopardize many valuable initiatives between industry and the universities

Recommendations

- Further improve ICH-HCP training and compliance of investigators
- Further improve collaboration between industry and universities
- Create better collaborations with other EU countries and together strengthen the position of Europe as a clinical trial region. It is more advantageous to look for international collaboration and let other countries learn from our specific strengths than to strengthen our position as a single country

- Increase awareness at hospitals on ongoing clinical trials and incorporate the clinical trial process into the hospital culture
- Increase awareness of the benefits of participating in a clinical trial

O.B. Jochems, MD (MediServ)

25 August 2010, Eindhoven

Name: Odette Jochems, MD

Organization: MediServ

Title: CEO

Description of the Organization: MediServ was the first Contract Research Organization (“CRO”) established in the Netherlands and was founded thirty years ago (1980) by Dr. Jan Janbroers. MediServ is a small, full service CRO, involved in phase II, III and IV trials and provides assistance for Phase I trials in different countries in Europe. The monitoring by MediServ takes place in the Benelux. Through the membership of the Pharmaceutical Services Network “PSN” (a network of CROs in Europe) these services are also provided across Europe, Africa and the US. Throughout its lifespan, MediServ has performed trials in many different indications, such as arthritis and associated rheumatic disorders, cardiology, CNS, medical devices, NSAIDs and urology. MediServ was one of the driving forces behind the establishment of the ACRON (Association of Clinical Research Organisations in the Netherlands) and is a co-founder of the above mentioned PSN network.

Professional background and role in organization: Dr. Odette Jochems is a general practitioner by trade and joined the company in 1982. She started out as a field monitor, was later a CRA and Project Manager, and in 1991 she became CEO of the company. She continues to work as a general practitioner.

METC approval process

The biggest single weakness in the Dutch clinical trial environment is the slow METC (*Medisch Ethische Toetsings Commissie*) approval process. Dr. Jochems has observed a clear difference between the process and timelines employed by the Dutch and those used by the Belgians. In Belgium, submissions to the local METCs have to be made simultaneously and local METCs must provide their comments to the central METC within 30 days of submission. If the local METC fails to submit the required documents within this timeline, the central METC will not consider it for participation in the study. The central EC does not allow the local METC to provide comments on anything other than patient information and the local feasibility of the trial. As a result, in Belgium, the METC approval process is always finalized within two months of the simultaneous submission to local METCs.

In the Netherlands, regulations are in place regarding the timelines. However, local feasibility committees are, besides checking patient information and the local feasibility, also interfering with the protocol. In the opinion of Dr. Jochems the committees do not feel any pressure to abide by the timelines. The Netherlands participates in an international clinical trial environment within competitive enrolment conditions. Often the inclusion period will end with only a few patients enrolled in the Netherlands, and in the worse cases, ends with sites that have not even been initiated yet. As a result, the sponsors of clinical trials are beginning to ignore the Netherlands when making a selection of countries in which they wish to perform their trial. The sponsor in such case may still be interested in a Dutch Key Opinion Leader taking a position in a Steering Committee, but, the actual research is performed elsewhere.

A solution could be to implement the same approach as used in Belgium, and provide the central METC with the tools to put pressure on local feasibility committees in order to better control the timelines. If the situation is not improved soon, the Netherlands will lose a lot of business to other countries and risk its competitive position in Europe. Making the METC approval process less time consuming will improve the Dutch clinical trial climate considerably.

Effects implementation EU CTD⁴

Dr. Jochems has not observed negative effects from the implementation of the EU CTD. In her experience, the stricter requirements for trials paediatric trials and those involving orphan disease, do not influence the clinical trial environment in the Netherlands.

Data Protection

The impact of the new data protection requirements further to the European Data Protection Directive are not yet visible. Other countries in Europe are focusing more on compliance in this respect: e.g. in Germany the Patient Informed Consent includes a large section on data protection. However, in the Netherlands this is not (yet) the case.

Standardization of clinical trial documents

There is no need for the further standardization of clinical trial documents. A standard clinical trial agreement will often be unhelpful, since US based sponsors that do not have a local subsidiary in the Netherlands usually insist on using their own template anyway. Further, it is usually very difficult to influence the hospitals lawyers in the negotiation process.

⁴Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

The quality of clinical research in the Netherlands

According to Dr. Jochems the Netherlands' biggest strength as a clinical trial country is that is that historically the country has been renowned for *experience, expertise and quality of clinical research* and the *availability of many key opinion leaders*. In her experience, these factors are important when a sponsor wishes to perform a clinical trial and this is why they are selecting the Netherlands for their trials.

Costs

Since MediServ is part of the PSN, Dr. Jochems is aware of the costs of clinical research in the different European countries. The costs for performing a clinical trial in the Netherlands compared to other European countries are standard and in line with the costs in Germany. It is cheaper than performing a trial in the UK or the Nordic countries. However, the Netherlands remains more expensive than the Southern European countries. Dr. Jochems' experience is that costs are not the most important factor for a sponsor, and that the quality of the clinical trial services are often decisive.

Recruitment and motivation of investigators

The sponsor often wishes to work with certain names in the field, who can then assist with the further recruitment of the investigators for the trial. In the Netherlands, you often end up with the same group of specialists for the same indication. Specialists are often not very motivated to participate in a trial. Dr. Jochems notices a clear difference in the willingness to participate in a clinical trial between specialists in Belgium and the Netherlands. Because of the better economic situation of specialists in the Netherlands they are not eager to spend time on a clinical trial, unless they are very well paid for it. In Belgium, the specialists need the money to finance their clinical trial organization.

For studies involving a general practitioners ("GPs") it also proves difficult to recruit investigators. The GPs are too busy with all their administrative obligations. For them, participation in a clinical drug trial is really an additional burden. In addition, they are usually not specifically interested in the pharmaceutical industry and innovation.

Training and education investigators

The educational level of investigators in the Netherlands, is in general, is very good. However, investigators are often not aware enough of the ICH-GCP requirements. That is why part of the investigator meeting is always dedicated to ICH-GCP training.

Access to well-trained CRO staff

MediServ was always able to find good-quality staff. However, low turn-over rates hamper solid general statements on this topic.

Infrastructure hospitals

Currently clinical trial desks are located within the hospitals. The desks can assist in many aspects of the clinical trial process within the hospital. The research nurses are usually very well educated. It is beneficial for both the investigators and the industry that they can assist the investigator and take care of the daily tasks. This in general leads to high quality data. It is also easier for companies to contact the research clinics: the investigators often have busy schedules and the research nurse can act as a first point of contact for other parties.

Clinical trial desks can also play a role in the site agreement negotiations: the lawyers at a hospital often do not feel a sense of urgency when reviewing the site agreements and it is very difficult to contact them directly. Of course their support would make the whole process more efficient.

Recruitment of study subjects

The Netherlands does not have access to a big pool of patients because of the population of the country. In addition, the high level of our health care system hampers quick and easy enrolment of patients for clinical drug trials. Furthermore, the recruitment of patients is very difficult if patients have to be taken off their existing treatment plans. Any departure from existing treatment plans is not welcomed by either the patient or the investigator.

A thorough feasibility study is crucial, focusing on the study design and indication to avoid producing disappointing patient recruitment rates. When in doubt, a site should not be initiated, since it could result in the loss of a large outlay if subsequently no patients are involved.

Patient networks are not very helpful, since they only collaborate within their own pool of acquaintances, and are not accessible to all parties in the industry. For studies with indications such as flu and bladder infection, where patients can only be found with the GPs, it is better to collaborate with a Site Management Organization (“SMO”) that has a good idea on the planning, has good recruitment system in place and has access to a pool of patients through a group of adherent GPs.

Collaboration industry, CROs and academic hospitals

It is helpful to have a clear division of responsibilities between the different players in the clinical trial industry. Risk sharing enterprises between sponsors and CRO can be difficult in respect to possible conflicts of interest. However, the interaction between industry, CROs and academic hospitals is generally are desirable and productive .

The value of Dutch organizations

Organizations such as ACRON, DCTF and Nefarma have benefitted in the clinical trial environment. Nevertheless, further improvements remains necessary. The organizations should try and obtain a larger influence with the Dutch government and other bodies that have authorization to change practices in the clinical trial process within the Netherlands.

Trends in clinical research

The past years cardiovascular studies were very popular and now oncology and paediatric trials have become more important for the industry. Oncology trials in the Netherlands have been especially successful due to the great infrastructure and governance in this area.

The effects of globalization

The effects of Globalization highlighted by Organon (MSD) is a by-product of the acquisition of Dutch companies by foreign pharmaceutical companies. The foreign companies are moving their R&D divisions to their head offices, where key decisions are made. The local affiliate is then often only used for selling activities or the executive part of clinical research, which has little influence on protocol. These activities are not important to a scientist or investigator. Scientists will be drawn to head office locations that are found out with the Netherlands where interesting R&D is being undertaken and therefore they will be able to contribute scientifically. Since our scientific quality is at present one of the Netherlands biggest strengths, This a serious threat for the clinical research climate in the Netherlands.

The role of the Dutch government

The government should act pro-actively and not reactively, as they did with Organon (MSD). If the government wishes to maintain the knowledge economy found within the Netherlands, the government should strive to keep important R&D divisions in the Netherlands. At this stage the government has little influence on the decisions made at the head office of the pharmaceutical companies.

SWOT Analysis

Strengths <ul style="list-style-type: none"> • The access to experience and expertise • The high quality of clinical research • Availability of many key opinion leaders. 	Weaknesses <ul style="list-style-type: none"> • The slow METC approval process
Opportunities <ul style="list-style-type: none"> • The oncology governance and infrastructure is very good: oncology trials are important research area • Increased use of research desks in hospitals 	Threats <ul style="list-style-type: none"> • If we do not improve the situation with the METC approval process, sponsors will skip the Netherlands as a country to perform their therapeutic confirmatory trials in • Our strength comes from the high level of expertise in our country, however, globalization may result in a leave of high level investigators who will move to the interesting R&D locations elsewhere in the world (quality will disappear abroad)

Recommendations

- Improve the METC approval process in accordance with the “Belgian model”: simultaneous submission to the local ECs (ethical commissions) with strict timelines and requirements for the local feasibility assessment (20 days) and strict timelines for the central METC (28 days).

A.F. Cohen, MD PhD FFPM (CHDR)

26 August 2010, Leiden

Name: Adam Cohen, MD PhD FFPM

Organization: Centre for Human Drug Research

Title: CEO (Director)

Description of the Organization: CHDR is a full service contract research organization (CRO) that provides a full spectrum of high quality clinical pharmacology services to the (bio-) pharmaceutical industry. CHDR specializes in data-intensive, early phase, clinical studies where pharmacokinetic and pharmacodynamic parameters are obtained (studies first-in-humans PK/PD modelling proof-of-concept). CHDR has a wide-ranging, self-funded research program where biomarkers are explored for pharmacological responses or other indicators related to a therapeutic intervention. In addition, CHDR employs medical experts who leverage their pharmacological know-how to efficiently guide the drug development process.

Professional background and role in organization: Since 1987, Cohen has been the director of the Centre for Human Drug Research (CHDR). He is professor of Clinical Pharmacology at Leiden University and has a clinical attachment at the department of nephrology at Leiden University Medical Centre. He is vice-chairman of the Central Ethics Committee and the Competent Authority (CCMO) of the Netherlands and European editor of the British Journal of Clinical Pharmacology as well as a member of the Health Council of the Netherlands and the Council for Medical Sciences of the Royal Academy of Sciences of the Netherlands.

METC approval process

Slow local feasibility assessments are a delaying factor in the METC approval process in the Netherlands. This problem cannot be solved by adding further regulations or by implementing better compliance measures. The basis of the problem can be found in the lack of strategic overlap between the hospitals and the industry. At the level of the hospital boards and the local feasibility committees there is no sense of urgency or motivation to participate in clinical trials, especially if the trial is sponsor initiated. In addition, there appears to be a lack of trust between the different METCs, which results in a situation where all METCs wish to go through a complete and thorough assessment procedure at the same level of intensity as was done by the other METCs.

There is however a gradual progress visible with respect to the local approval process. Levels of trust between the different METCs are slowly improving and local METCs have come to

realize that it is in the best interests of the hospital to make the process more efficient (e.g. the METC of the Erasmus MC in Rotterdam abolished de “hertoetsing”).

Effects implementation EU CTD

The EU CTD was successfully implemented into Dutch law (the WMO); the interpretation of the EU CTD was completed in such a way that it did not produce many additional requirements for performing a clinical trial in the Netherlands. Adam Cohen has been leading the implementation committee.

The CA approval process in the Netherlands is superior to other such processes anywhere else in the world; in the Netherlands there no longer exists the dual approval process (thus no involvement of governmental bodies) as is the case in many other countries. The current system in the Netherlands can now handle the entire range of disciplines: from gene therapy studies to very simple generic studies.

A potential threat could arise if European regulations are further harmonized and METC approval is arranged at a European level. If for example, Dutch investigators need to get approval in another country in Europe to start their clinical trial, the issues that affect the obtaining of local approval would then be applicable on a European level. As the situation slowly improves in the Netherlands, it is recommended that focus should first be placed on further improvements at a local level.

In general, it would be inaccurate to think that the EU CTD could completely harmonize the clinical trial system in Europe, since the European countries show substantial differences in areas such as medical practice and health care systems.

Data Protection

In the Netherlands, the observation of data protection compliance is not yet particularly strict. There should be a better collaboration between the different players in the clinical research area to ensure compliance.

The quality of clinical research in the Netherlands

The Netherlands is a small country with a relatively high scientific output. The ability to deliver large quantities of patients may not exist, but the delivering of knowledge and expertise is an area of strength. The Netherlands also offers a relatively high level of infrastructure: the hospitals are of homogenous quality and we have excellent universities. In addition Dutch investigators have a tendency to collaborate on a global scale, which facilitates exchange of knowledge and visibility of their quality internationally.

Recruitment and motivation of investigators

It is difficult to generate enthusiasm in investigators for participation in therapeutic confirmatory studies. Direct patient health care is often considered more important and the investigators usually already have a high work load. Financially and scientifically these types of studies are not appealing and interesting enough in many cases, especially if there is no possibility for publication.

Training and education investigators

The clinical research environment in the Netherlands is known for its high level of scientific education and the expertise of the investigators. The different players in the clinical research area should take responsibility for offering the necessary training and education to staff that is required to perform high level clinical research. The CHDR for instance is starting a course for nurse practitioners and is continuously training clinical pharmacologists.

Currently, there are insufficient possibilities provided by the mainstream educational system to properly train and prepare staff for clinical research. If the aim is to create a country where top clinical research is performed, we should strive for further improvement. There is, at the moment, too little collaboration and a lack of vision on an integrated country-wide scale with respect to the education of the required investigators and clinical research staff.

Infrastructure hospitals

Certified research units in hospitals would improve the clinical trial environment in the Netherlands. Such units cause the clinical research process in hospitals to be more efficient and it creates a better facilitation for sponsors and CROs that perform clinical trials in the Netherlands. If a hospital can create a situation that generates income for future research and for managing such a research unit, it becomes more appealing for hospitals to participate in clinical trials, even in the generic ones.

Recruitment of study subjects

Due to the size of our country and the high standard of care, the Netherlands is not an attractive country for recruitment large numbers of patients. From that perspective, performing a therapeutics confirmatory trial in the Netherlands might not appear very interesting to the industry. However, looking at the data that is available from the CCMO, around 100.000 patients per year are recruited for clinical research. This number stays fairly stable and is quite a high number for such a small country.

Recruitment of patients or healthy volunteers at the CHDR is mainly achieved through advertising. There are no visible effects of the possible negative image of clinical research

when recruiting study participants. The infrastructure for recruiting patients could be improved. Raising awareness in potential patients on the importance of (participating in) clinical research should in this respect also be taken into consideration.

Collaboration industry, CROs and academic hospitals

If the Netherlands would like to become a more important player in clinical research, it must be ensured that it reaches the status of an excellent clinical research country, with a high level of expertise and clinical research service. In order to achieve this, industry and the government have to create a better strategic collaboration between the industry and the investigators.

The value of Dutch organizations

That there are organizations in the Netherlands that focus on the improvement of the local clinical trial climate is a valuable state of affairs. The issue is, that often the problems that exist are not approached in an integrated way and consideration of the complete clinical research area is lacking. Further, because everybody agrees on what needs to be done differently, there is no sense of urgency driving solid action. There is no perception of *what is required* to do things differently and improve the infrastructure, because no solid analysis has been made of the existing problems. As a result, the right parties are coming together, but there are no important results visible.

Trends in clinical research

Adam Cohen does not yet see many innovations that offer the possibility of shifting the clinical trial process substantially more to the pre-clinical phase. Organ techniques are not sophisticated enough and are will never be able to provide such a complete picture of a complex organic model as is provided by animal and human testing. The Dutch clinical trial environment is very well equipped and developed for this type of pre-clinical and early stage clinical trials.

The effects of globalization

Sponsors are now looking at clinical research on a global scale. Regions, such as Latin-America and Asia, that are more cost efficient, but also are gradually have become sufficiently developed to perform therapeutic confirmatory trials and are able to deliver large quantities of (treatment-naive) patients are becoming more interesting for pharmaceutical companies. Since the Netherlands is more expensive compared to the countries in these aforementioned regions and has a (relatively) small amount of patients available, it is not very appealing to a sponsor to outsource this type of research (recruitment of large numbers of patients and straight-forward data collection) to the Netherlands.

Further, the industry links their investments in clinical research to revenues, and as such we are not a very interesting country as the Netherlands represents only a small market. Adam Cohen has the opinion that the industry should look at it differently if they wish to improve clinical research: the Netherlands is an appealing country when it comes to delivering the infrastructure, the expertise and the knowledge.

Pharmaceutical companies often state that the Netherlands is a research unfriendly country, since it is difficult for a pharmaceutical company to get its drugs on the market. Mr. Kortlever from Organon (MSD) has presented this as one of his central arguments when defending the decision of the Organon (MSD) board to shift the R&D unit to the head office in the US. Adam Cohen however feels that this argument is not directly related to the fact whether the Netherlands is a research friendly country or not, and therefore the difficulty for a pharmaceutical company to get a drug on the market has to be considered in a separate discussion.

The role of the Dutch government

Adam Cohen has the opinion that the governments' options were limited with respect to managing the Organon (MSD) situation. Decisions of a large multinational such as Organon (MSD) with respect to its company strategy are made at the head office and are based on the requirement to remain competitive. The costs for keeping the R&D unit open via government investment are simply too high in relation to the potential revenues generated by the R&D unit, and therefore not worth exploring further.

SWOT Analysis

Strengths

- Good CA approval system
- Excellent level of scientific education
- High quality investigators and research staff
- High and homogenous level of quality of the hospitals
- Cultural tendency to international collaboration
- Reasonable and civilized health care system

Weaknesses

- Local feasibility assessment is a delaying factor in the METC process
 - Low motivation for investigators to participate in generic trials: financially and scientifically unappealing
-

Opportunities	Threats
<ul style="list-style-type: none"> • Do not focus on one aspect of clinical research, but approach it as one integrated process. Stimulate collaboration of the different players in clinical research, by offering a common goal • Further develop the trend of establishing research desks at the hospitals 	<ul style="list-style-type: none"> • Further European harmonization through the revised EU CTD, which will further complicate the clinical trial process • Globalization results in the migration of quality

Recommendations

- Further improve the local feasibility assessment and the participation of investigators by creating a better strategic overlap of the objectives of industry and investigators
- Hospitals should receive incentives and support to install research desks
- The Netherlands should differentiate itself from other countries by offering a high level of infrastructure and services, with Switzerland as an example

A. Huisman, MSc (PRA International)

7 September 2010, Zuidlaren

Name: Arnoud Huisman, MSc

Organization: PRA International

Title: Vice President Clinic

Description of the Organization: PRA International (PRA) carries out world-wide clinical research on the efficacy of medicines in humans for pharmaceutical and biotech companies. In the Netherlands PRA (formerly Pharma Bio-Research) has 450 employees divided over four locations in the Northern part of the country PRA performs clinical and bioanalytical research, from first-in-man until proof-of-concept studies. In Nieuwegein PRA also has a small unit for project registration (phase II and III) studies.

Professional background and role in organization: Arnoud Huisman has worked as Director Marketing & Sales at Wyeth Pharmaceuticals from 1998 to 2004, and has worked as Vice President Clinic at PRA International in Zuidlaren since 2004. He has been board member of the ACRON since March 2008.

METC approval process

In the Netherlands, the regulatory timelines for Phase I trials are very favourable: it usually takes only 2 weeks to obtain approval. This is particularly swift when compared to Germany, where it takes 60 days or France, where it takes 3 weeks. In the US it takes 3 months to open an IND (Investigational New Drug). For early phase trials, which are not usually long term trials, this makes a considerable difference to the total duration. The fast approval process is due to the fact that, the decision making power remains with the local METC and the CCMO is only involved administratively. The CCMO has to follow the timelines of the local METC, and the maximum time allowed by law is 60 days. This competitive position is threatened by discussions concerning the arranging the METC approvals at a European level: a mutual recognition system might lead to equal timelines for the EU and therefore no more advantage for the Netherlands.

Effects implementation EU CTD

The competitive position of the Netherlands with respect to the brief time period required for obtaining METC approval is a direct result of the implementation of the EU CTD (also see above). It has taken some effort to convince sponsors that, the implementation of the EU CTD did not have big impact on the Netherlands. The CA process is little more complicated than

before, and sponsors are nervous that, under the relevant implemented laws they will have to submit the Investigational Drug Brochure (containing confidential information) to a local METC without any control on confidentiality of individual members. For that reason sponsors sometimes go to Switzerland, since the EU CTD is not implemented there.

The quality of clinical research in the Netherlands

Despite the high costs (see below), sponsors are interested in performing clinical research in the Netherlands, due to the excellent scientific level of clinical research evident within the country (e.g. more experienced than in the US): Dutch professionals can assist with protocol designs and can apply their extensive experience.

Costs

The costs for a Phase I study are high compared to the other EU countries and the US. PRA is relatively expensive for a sponsor: healthy volunteers come from all over the country and travel reimbursements are therefore relatively high. Labour costs in the Netherlands are also relatively high.

Recruitment of study subjects

PRA recruits healthy volunteers to test the safety of a compound and to test patient efficacy. Patient recruitment is a difficult task in the Netherlands. PRA is dependent on specialist referrals. These specialists often wish to keep such patients for the industry sponsored (phase II-III) clinical trials that they are participating in. PRA does not collaborate with first line of care for patient recruitment.

PRA has its own recruitment agency and recruits between 2000 and 3000 subjects per year for their clinical trials (about 10% consist of patients, the remaining part are healthy volunteers). Recruitment of healthy volunteers is easier to achieve thanks to the use of advertisements and the (good) volunteer participation reimbursement. For a sponsor, the access to patients is more important than the costs. Patient recruitment is not hindered by a negative image of clinical drug trials, but rather by a lack of awareness.

Collaboration industry, CROs and academic hospitals

PRA currently does occasionally collaborate with hospitals. It is not possible to perform oncology trials in the Phase I unit because, patients need to stay in the hospital environment where they are treated. A potential option therefore, could be greater collaboration in order to create a Phase I setting in the hospital and deliver the equipment and resources needed to perform the trial. In the Netherlands, this creates all sorts of liability issues between the parties, and therefore this is done by PRAs subsidiaries in Central Europe.

It would signal a marked improvement if specialists and hospitals were to show more interest in Phase IIa Proof of Concept research: if this does not change, it is likely, that this type of clinical research will move away from the Netherlands. It is remarkable that early stage (ground-breaking) clinical trials do not appeal to investigators. Later phase studies are apparently more interesting for the investigators.

Access to well-trained CRO staff

PRA finds it hard to attract qualified staff, due to its location in the North of the Netherlands. When the search for personnel is successful, employees tend to stay at the company for a long time. A low turn-over rate is of course very favourable for the continuity and preservation of knowledge for a company. With respect to recruiting qualified research nurses there is some competition from the hospitals in Groningen.

The value of Dutch organizations

Organizations like the ACRON and DCTF are gradually becoming more important in the clinical research arena. They accomplished the feat of getting different parties in the clinical research environment to the table for discussions. However, at this stage the improvements they have made to the clinical research climate are not yet visible in daily practice when compared to other countries. The CCMO recently initiated a discussion on the concept that all research data should be published in the CCMO database, even before a study has begun. The CCMO requested the opinion of Nefarma, but did not contact ACRON, although this idea would have had a directly negative effect on Phase I research mainly conducted by Dutch CROs. This indicates that the contact between ACRON and CCMO should improve as ACRON governs the interests of the Dutch CROs. On the other hand, if the public health inspector has questions on Phase I research, he does contact the ACRON which is a promising sign.

The conclusion reached here, is that there has been some visible progress, but the DCTF and ACRON have to strengthen their position relative to the government, the CCMO and other authorities.

The development of the mutual recognition of METC approvals in Europe may present a putative threat for Phase I research in the Netherlands. Currently the Netherlands holds a strong position because of the short timelines required for METC approval for phase 1 studies. With the mutual recognition the durations to start a trial may get longer which could harm Dutch CRO's like PRA. Currently, PRA is the biggest employer in phase I clinical research in the Netherlands and with regard to Phase I research they are a top-three player in Europe in volume. For the purpose of keeping the strong position of PRA in the clinical research arena, preventing the aforementioned harm, PRA must remain a strong organization with

international connections and authority. The CCMO could influence this decision, and it is recommended that they collaborate with organizations such as DCTF and ACRON.

A further problem exists in that, within the Netherlands there are numerous different organizations working on their own individual problems and failing to join forces. Life Sciences & Health could be an example of an organization that actually has been able to construct a bridge between life science and health (biotech and development) and also should include the CRO industry in their initiatives.

Trends in clinical research

There will be an increase of insourcing knowledge by industry, especially with respect to Phase I knowledge. This of course is an interesting development for PRA (and other Phase I units in the Netherlands). Further, clinical research will be performed sooner on patients (rather than additional studies in healthy volunteers).

The shift to early, pre-clinical studies due to new organ techniques is not to be expected: eventually testing on humans is required to generate the desired data. Small steps will be made (e.g. with cell-lines), however, it will always be through a surrogate and all the research needs to go through the required phases anyway.

The effects of globalization

There has been a clear shift visible towards the emerging markets for Phase I research: 20 years ago 60% of Phase I research was conducted in Europe and 40% in the US. 5 years later this had changed to 60% in US and 40% in Europe; the current figures sit at 30-35% in Europe, 40-45% in the US and 10-20% in Asia and LATAM. External cost savings will be levelled out by the high number of internal costs required to manage the studies in these new countries. Therefore, the reason for the shift can not only be attributed to cost efficiency, but mostly to the fact that these countries provide much better access to patients.

The situation regarding Organon (MSD) is, in the short term very unfavourable. However, in a year or two, these circumstances will result in an increase in outsourcing by the company which will of course be beneficial to the CRO industry.

The role of the Dutch government

It would be helpful for the industry if the government appealed to the Dutch people to take responsibility to collaborate and participate in improving health care, although it will be difficult to convince people in the Netherlands (look at e.g. the donor codicil). The decision to close-down the R&D unit of Organon (MSD) could not be prevented by the government, since it

is very difficult to interfere in the decision making of a multinational company. TI-Pharma has been a very valuable government initiative. However, the lack of financial continuity makes it impossible to build a proper knowledge based economy. An alternative could be to use governmental funding in the start-up phase and to search for external sponsoring to ensure continuity and independency.

SWOT Analysis

<p>Strengths</p> <ul style="list-style-type: none"> • For Phase I trials RA and METC approval timelines are very good compared to other countries • Excellent scientific level in clinical research 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Limited long-term continuity of the government to the knowledge economy
<p>Opportunities</p> <ul style="list-style-type: none"> • Strengthen the position of organizations like the ACRON and DCTF towards the government, the CCMO and other authorities • The development that more Phase I knowledge will be insourced 	<p>Threats</p> <ul style="list-style-type: none"> • Mutual recognition system of METC approvals at a European level • Lack of interest by specialist in participating in early phase (phase IIa) studies, this type of research will disappear in the Netherlands • Shift to emerging markets for better patient recruitment

Recommendations

- Prevent the further centralization of the METC approval process in Europe in order to keep our competitive position with respect to the timelines for performing Phase I trials in the Netherlands
- Improve the position of the Netherlands as clinical trial country by further strengthening the position of organizations like ACRON, DCTF and Life Sciences & Health

Ms. L. Becker (Quintiles)

8 September 2010, Hoofddorp

Name: Lisa Becker

Organization: Quintiles

Title: VP, Integrated Patient and Site Strategies and General Manager, Quintiles BV

Description of the Organization: Quintiles is the only fully integrated bio and pharmaceutical services provider offering clinical, commercial, consulting and capital solutions worldwide. The Quintiles network of more than 20,000 engaged professionals in 60 countries around the globe works with an unwavering commitment to patients, safety and ethics. Quintiles helps bio pharmaceutical companies navigate risk and seize opportunities in an environment where change is constant. Quintiles BV works on international, multi-centre trials across many therapeutic areas.

Professional background and role in organization:

Lisa Becker has been with Quintiles since 2007, and is currently Vice President, Global Head of Integrated Patient & Site Strategies and General Manager of Quintiles BV. Lisa studied biology and public health, and began her career in clinical research in 1984 as a physician assistant. She relocated to Europe in 1989, and has since held several international positions, gaining over 20 years of experience and expertise in biotechnology, pharmaceutical, medical devices, and academic research and product development.

METC approval process

Since the implementation of the EU CTD in 2006, the METC approval process has become more cumbersome and slow in the Netherlands. Before implementation, regulatory approval generally took between 30 and 60 days, whereas now, approval timelines are substantially longer. This makes the Netherlands less attractive as a location to sponsors of international studies with precise recruitment timelines,

To achieve the goal of healthier humans by getting new and better medicines to patients, faster, all stakeholders including policy makers, regulators, and sponsors should be working better together. They should be made aware of the value of each of their contributions. With the addition of stakeholder groups and multiple layers (i.e., local ethics committee), conflicting interests have developed while there should be a common competitive interest.

Effects of EU CTD implementation

Since the implementation of the EU CTD, there has been a substantial and visible increase in bureaucracy and the METC approval process has become very slow (see above). Neighbouring countries such as Belgium are performing much better in that respect, because their approval process is highly streamlined.

Negotiating site agreements

Site agreement negotiations need to be in place very quickly when starting up a clinical trial in order to meet tight recruitment deadlines. Hospitals often have multiple layers of authority (the Principal Investigator, the hospital board, the department, the laboratory, the pharmacy, etc.) all of which can contribute to an inefficient and lengthy process. Sites with a solid commitment to clinical research often perform better because they have established infrastructure and streamlined processes. Sponsors should consider criteria such as this alongside their normal feasibility assessments when choosing sites.

The quality of clinical research in the Netherlands

The Netherlands has traditionally been one of the best countries for medical care, due to the number of expert clinicians, a focussed public health policy and practice, good access to care, research/tech savvy population, and excellent networks for patient recruitment and specialist centres. By extension, it was also considered a good clinical trial country. However, the quality of clinical research is increasingly considered in the potential future market. And, despite the excellent clinical care, not all investigators and their study staff are trained in and understand the impact of Good Clinical Practice (GCP). In that sense, the Netherlands has some work to do, and is comparatively less appealing.

The Netherlands has very good infrastructure in place for healthcare records. This facilitates access to important population data for sponsors, which makes feasibility and patient recruitment more streamlined. It also allows access and collection of valuable research information (e.g. clinicalresearch.com, iGuard, Provenance).

The Netherlands is known for its numerous key opinion leaders, and often this is what attracts a sponsor to a particular site. However, the participation of key opinion leaders is not always beneficial to the conduct of a trial (see below).

Recruitment and motivation of investigators

One of the strengths of Quintiles is its rigorous site selection, based on historical quality and recruitment data, systems and processes, and epidemiological data. One issue in the Netherlands has been the lack of willingness by sites to adopt a more research-friendly

approach. Key opinion leaders are usually the motivation for a sponsor to bring a trial to the Netherlands; however the sites in which they work may not have the quality systems and processes to support the trial.

In order to keep the Netherlands an interesting and appealing country for the sponsor, it is important for KOLs to be more demanding of (their) sites to ensure that are set up to support clinical trials. Quintiles collaborates with the top-clinical hospitals (STZ hospitals) since they are putting effort into process optimization and are delivering high number of patients and good quality data.

One way to foster more involvement in a clinical trial by an investigator is to offer the opportunity to pursue sub-studies. This will increase the value of the clinical research and enable the investigator to gather data for a publication.

Quintiles works with a large network and database of 3.000 General Practitioners and it is not difficult to recruit GPs, especially for a study with an interesting indication or new compound. It is important however, to develop good working relationships with GPs and provide support throughout the duration of the study, to ensure that they remain engaged and can manage the increased demands of a clinical trial alongside their busy practices.

Training and education investigators

The training of Dutch clinical trial staff in ICH-GCP is good compared to other countries, and is continuing to improve. CROs and pharmaceutical companies alike are training investigators and research nurses in ICH-GCP guidelines. Furthermore, the implementation of the BROK-course for academic hospitals has improved and ICH-GCP has been implemented in some Master study curricula (e.g. Health Sciences at the VU).

The number one country in ICH-GCP education and compliance is the UK: they have many different institutes and requirements to support this standard. To replicate this in the Netherlands is perhaps not necessary and it could lead to additional hurdles or delays when performing a trial. However, training of PIs and study staff, and creation of research environment and infrastructure within the institution is key to continued success and further growth.

Infrastructure hospitals

Hospitals that have established infrastructure and experience in conducting clinical trials produce better results. Key to this is having research desks in the hospitals, which become the

multidisciplinary platform for research, organization and administration of trials, streamlining the process and improving productivity, and facilitating interface with PI and study staff.

Recruitment of study subjects

Access to patients is extremely important to Quintiles and its biopharma customers and is a key factor in determining where to conduct a study.

In general, a drop in patients per site has been visible in recent years in North America and Western Europe, which has made sponsors more inclined to go to emerging markets where patient recruitment is less challenging. Patient recruitment metrics are particularly low in the Netherlands, perhaps because of its relatively small patient population, and competitive research studies.

Quintiles drives patient recruitment through a focus on therapeutic areas and through collaborating with sites in its prime and partner-site programme. This includes:

- a.) A thorough review of investigators, before the study starts, to determine recruitment expectations and plans including a review of specific patient pathways. For phase IIIb chronic disease studies the Netherlands has performed drastically better than other countries because of this approach
- b.) Quintiles gives special attention to certain sites (prime sites) by providing support in developing systems, processes and infrastructure that is conducive to clinical trials
- c.) In addition, Quintiles has established collaborations with “partner sites”, which are recruited because of their high standard of quality and commitment to clinical research.

The infrastructure for patient recruitment for late phase trials is good. In diabetes, hypertension and cardiology for instance, recruitment is brilliant due to the many patient organizations, and collaborative physician organizations that facilitate patient recruitment.

Collaboration industry, CROs and academic hospitals

There is a need for clearly defined roles in the clinical research industry and stakeholders should respect each other’s work. However, they should at the same time cooperate extensively and where possible create synergies. Quintiles works with Bio-tech companies in venture capital collaborations: they assist them with research, and share the risks and the profits.

Access to well-trained CRO staff

The Netherlands has a very competitive market when it comes to finding talented, qualified and trained clinical research (monitoring) staff. The high salaries, the good secondary labour conditions and the competition make it difficult to attract and retain candidates. Economic drivers have led to consolidation, and several smaller local CROs are merging with the global CROs – resulting in a more full-service offering as opposed to single (monitoring) service.

The value of Dutch organizations

Quintiles works closely with ACRON, DCTF, NVFG and other organizations. However the industry as a whole in the Netherlands could do more to achieve a stronger position for the country as a destination for clinical research.

The effects of globalization

Quintiles has noticed a shift to the East in the clinical trial activities (first to Eastern Europe and now towards Asia), due to downward pressure on cost, good patient recruitment and advances in quality standards in emerging markets.

Once the social and cultural challenges are overcome even more research will be conducted in Asia and the Latin American countries. The quality in these countries will also improve. In Eastern Europe start up is longer, but once a study is up and running, this is offset by fast patient enrolment, a huge patient population, lower costs and equal quality. Further East, one can benefit from a quick start up and lower costs, but the quality is not yet at acceptable consistently comparable level.

The role of the Dutch government

The government could support the clinical research environment by establishing clear rules on timelines and arrange for a less rigid interpretation of the EU CTD in order to promote the Netherlands as a competitive country.

Is the Netherlands an attractive country to establish your company

The Netherlands can be seen as a good place to start-up or expand a company. It is a gateway to Europe, has a relatively high number of university graduates and experienced professionals, and the tax benefits/structure for non-EU countries can be very attractive. However, there is also the perception that the Netherlands does not have a favourable environment in which to establish/operationalize a company: it has the highest percentage of part-time workers (male and female) in the world which some translate into the fear of less productivity, has a comparatively low number of female executives, and has employment law that favour the

employee. On balance, the Netherlands is a good place to set up operations – for both companies coming from established and emerging market countries.

SWOT Analysis

<p>Strengths</p> <ul style="list-style-type: none"> • Good infrastructure for Phase IV studies • Good standard of medical care • Favourable company tax regulations 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Relatively small patient population and market size • Increased bureaucracy due to strict interpretation EU CTD • Difficult site agreement negotiations • Increased ethics approval timelines
<p>Opportunities</p> <ul style="list-style-type: none"> • The Netherlands has infrastructure for phase IV clinical trials, and can be rolled out to broader population base (i.e., vaccine studies) 	<p>Threats</p> <ul style="list-style-type: none"> • Lack of research-friendly KOL mindset/site infrastructure • Increased costs • Industry trend moving research to the East

Recommendations

- The ACRON and other representative bodies should have a broader say (stronger lobby) in the rules concerning the conduct of clinical research in The Netherlands.
- The clinical trial infrastructure in the Netherlands (at multiple levels) should be improved.
- KOLs should facilitate closing the gap between excellent clinical care and excellent clinical research.
- There should be an increased focus on patient access themes: a high patient enrolment and excellent site relationships are essential for attracting clinical research.

H.J. Out, MD PhD (MSD)

6 September 2010, Oss

Name: Henk-Jan Out, MD PhD

Organization: Merck, Sharp & Dohme (MSD)

Title: VP Clinical Research, Women's Health & Endocrine

Description of the Organization: MSD B.V. is the non-American subsidiary of Merck & Co, Inc., and has been a leading company involved with innovative medicine in the Netherlands for over fifty years. In July of this year, following a thorough reorganization of their Dutch affiliate Organon, it was announced that all R&D activities in the Netherlands are to be stopped. At the beginning of September this decision was postponed until the end of the year, to further assess alternative business development opportunities.

Professional background and role in organization: Henk Jan Out has been working for Organon since 1992. Organon was acquired by Schering-Plough, and later by MSD. He started as the Medical Research Project Manager (Infertility) of the Clinical Development Department and is now working at MSD as VP Clinical Research, Women's Health & Endocrine. In addition, he is a professor of Pharmaceutical Medicine at the Radboud University Nijmegen Medical Centre.

Ethics committee (EC) approval process

For an international company, the METC approval process found in the Netherlands, is not the most arduous process such a company could face. To give some examples: in China it takes a year between protocol submission and study start. In Brazil it takes it also takes a significant period of time before the trial can begin. Yet, these countries remain very popular for industry-sponsored trials. The eagerness of the investigators to participate in clinical trials and fast patient recruitment are more important factors than the METC approval process. Obviously, a long period spent obtaining regulatory approval does not favour the Netherlands, because the industry prefers countries where the regulatory process is less cumbersome.

Effects implementation EU CTD

The implementation of the EU CTD did not have an influence on the competitive position of the Netherlands within Europe, since the effects of implementation do not widely differ from other countries where the EU CTD is implemented.

Negotiation of site agreements

Site agreement negotiations are not an important issue in the Netherlands, despite the fact that there is usually a little more discussion on the publication section than in other countries. However, troublesome contract negotiations at an international level can certainly be a delaying factor, especially now that hospitals have their own lawyers who amongst other things are often keen on more favourable intellectual property language for their client.

The quality of clinical research in the Netherlands

The Netherlands is performing very well on the clinical research front: there are high publishing figures, the country and its expertise are always well presented at the important conferences and there are also many key opinion leaders. The Netherlands is also very visible in clinical drug research with new compounds, and studies that need scientific input.

Costs

The Netherlands is not greatly expensive with respect to investigators payments when compared with the US for example. Scientifically educated staff are relatively cheap in the Netherlands.

Recruitment and motivation of investigators

Some investigators are not interested in industry sponsored confirmatory trials, due to the lack of a possibility for scientific input or authorship of publications. In contrast, other investigators can see the benefit of generating income from this type of study and use it for more interesting research. For example, one Dutch professor was involved in several large phase III studies with antithrombotics which generated enough income to set up two or three other types of research and also allowed the Professor to negotiate several sub-studies with the sponsor. For an investigator, a trial with a new compound is usually of interest. In general, Dutch investigators are better equipped and motivated for clinical trials that require scientific input (usually early phases), since they are more academically than operationally oriented.

For key opinion leaders it is easier to negotiate interesting terms for participation in a trial, such as sub-studies and publication rights. Furthermore, it is commonly known that key opinion leaders are good for PR (Public Relationships) purposes. However, such individuals are usually not very good performers in a trial and therefore it is important for a pharmaceutical company to find a balanced mixture of investigators that are able to deliver work of good quantity and quality. Investigators in the Netherlands are often somewhat presumptuous compared to investigators in e.g. the Asian countries, although the latter are also in the possession of high quality education and technology. Trials involving general practitioners are

usually not performed by pharmaceutical industries, since this is logistically very difficult (e.g. ensuring that all participating GPs are trained on ICH-GCP).

Training and education investigators

Education in the Netherlands is considered internationally to be of a very high standard. Knowledge of ICH-GCP by investigators is also improving (e.g. introduction of BROK-course⁵). The failure of the probiotics trial at UMCU⁶ revealed that universities in the Netherlands may very well underestimate clinical trial regulations, and it has made investigators aware that conducting trials is not a secondary task, but requires accuracy, commitment and preparation.

Recruitment of study subjects

An important consideration for the industry, when performing a trial at an international level, is to look for countries where patients are available. Although it is not the only factor that influences the decision, countries in Asia, Eastern Europe and Latin America (LATAM) are, (because of the availability of large amounts of treatment-naïve patients) from a recruitment perspective, more appealing than the Netherlands.

Collaboration industry, CROs and academic hospitals

There is a desire in the industry to collaborate more with universities in the mutual understanding of each other's objectives and interests.

Access to well-trained CRO staff

In a global pharmaceutical company, the decision to make use of a specific CRO is made internationally: for multi-country studies international CROs are always used and often there is a preferred provider relationship with such a CRO. It is therefore not really worthwhile attempting to put the Netherlands on the map as a good CRO country (for the later phase trials). Only in countries where there is not yet a great deal of experience (e.g. in Asia) is it especially important to collaborate with a high quality CRO that is excelling in the local market.

The value of Dutch organizations

Nefarma currently plays an important role in the ongoing discussions in the Netherlands, and maintains good communication and cooperation with the government. The DCTF still has to strengthen its position more, but is heading into the right direction.

⁵ Basiscursus Regelgeving & Organisatie voor Klinisch Onderzoekers (BROK)

⁶ The PROPATRIA-trial, a clinical trial performed from 2003 to 2007 to assess whether a pro-biotic supplement would decrease the chance of infection for patients with a "predicted severe acute pancreatic"

Trends in clinical research

Henk Jan Out expects that, in the near future, the emphasis in the clinical research process will shift slightly and focus on early clinical activities: pharmaceutical companies are eager to get greater security at an early stage as regards the effectiveness of a compound, since failures in the later phases of the drug development process are very costly. Translational medicine as such will become even more important and the Netherlands has a very strong presence in this area (CHDR, *Leidse farmaceutische wetenschappen*). Predicting pharmacodynamic effects is cost efficient and the Netherlands enjoys success in this area as it requires greater academic expertise (many of the Top Institute Pharma (TIPharma) projects are this type of trial).

The later phase confirmatory studies do not usually require much scientific input, and as such the Netherlands is not a very interesting country: “production work” will shift to low cost countries. Gradually our strengths (knowledge, techniques) become available in other countries that are eager for knowledge, are less expensive, can provide large amounts of treatment-naïve patients and in addition provide the opportunity to grow and have a large potential market. However, the cultural differences remain a significant hurdle when performing clinical research in the emerging markets.

Pharmaceutical companies are looking for a good “geo-mixture” of countries in which to do their trials. They will expect an environment which delivers good quality data and at the same time increases the chance for market access. Since the Netherlands is only a small country, and the pharmaceutical industry conducts its business globally, it is important to focus on international collaboration and not to build in additional hurdles that make us less attractive than other countries (stricter regulations, slow approval process etc.).

The international development that negative findings need to be published as well as the positive findings and that transparency is encouraged, is an improvement but could also be used for less constructive purposes.

The effects of globalization

MSD announced on the 8th of July this year that it planned to close the R&D unit in the Netherlands, a decision which has now been postponed until the end of the year. This could mean that interesting job opportunities in the industry within the Netherlands will cease to exist. The closure of the R&D unit in Oss could consequently result in a translocation of promising investigators that are educated in the Netherlands to very complex research topics abroad. Thus the knowledge that we have in the Netherlands would be used in countries abroad. It is obviously undesirable, if there is investment in the education of Dutch investigators and the Netherlands cannot benefit from the knowledge gained.

The role of the Dutch government

If the government wants a knowledge based economy, they will have to invest and make their objectives and plans visible. The establishment of TIPharma is an excellent initiative, and facilitates solid scientific research by a large number of investigators. The problem here is, that the funding for TIPharma is assigned for three years, and now that the government is under resignation (*MRT: at the time of the interview there was no new government yet*) a bridging advance of 6 million Euro is assigned, and the new government has to decide again how to proceed with the institute. However, if you want to use TIPharma to build your knowledge economy, you should show a long term vision and approach.

In other ways, the knowledge economy has not yet gotten started, because there is no willingness to invest, unlike in Finland for example, where investment has established Finland as a leading country in drug innovation. The government should link economic activities with scientific and healthcare activities. An example here is the example of MSD making a huge investment in the Netherlands by establishing a production unit for vaccines in Haarlem, which created approximately 200 jobs and the government subsequently decided to use the vaccine of a competitor in the vaccination program. Adequate collaboration between all stakeholders in the Dutch political system is therefore required. It will be attractive for a pharmaceutical company to invest in the knowledge economy and to provide employment in the Netherlands, if it knows that their medicines (after regulatory approval) will also be reimbursed.

Is the Netherlands an attractive country to establish your company

The government should link economic activities with scientific and healthcare activities (see above), make investments to boost the knowledge economy and establish favourable measures to make the Netherlands a more attractive country to settle for the industry. Company taxes are very attractive. However, local strict labour regulations may make it less appealing for foreign companies to invest and settle in the Netherlands.

The image of the industry is not positive and there is a wrong perception of how the industry performs its trials. Some powerful individuals constantly present their negative opinion on the industry in the media and seem to forget the positive contribution the industry has on health care (e.g. AIDS is now a chronic instead of a lethal disease due to innovative anti-HIV drugs)).

Furthermore, in the Netherlands it is difficult to get a compound on the list of medicines that are reimbursed by insurance companies. An additional hurdle for pharmaceutical companies is that general practitioners are reluctant to prescribe new compounds, since they are only just on the market, and long-term safety data is not yet available. This attitude of many Dutch GP's is working against innovation and is discouraging and damaging for the industry.

SWOT Analysis

<p>Strengths</p> <ul style="list-style-type: none"> • Many publications • Many investigators with special expertise/Key Opinion Leaders • Not particularly expensive if compared to other countries • High quality of education • Favourable company tax system (is appealing for a company if establishing an office) 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Not a large patient population available • Not a strong “production” country • No long term vision from government on knowledge economy • Lack of collaboration at government level to link economic and scientific and healthcare activities • Rigid labour law (scares away potential local subsidiaries) • Image of the industry is not good, due to politics, media and some individuals from the academic world • GPs reluctant to prescribe innovative (registered) medicines
<p>Opportunities</p> <ul style="list-style-type: none"> • The shift to early stage translational medicine: the Netherlands is good at this type of studies • Better political collaboration to make the Netherlands an appealing country for the industry to invest in • Further improve ICH-GCP compliance • Collaboration between industry and academic hospitals 	<p>Threats</p> <ul style="list-style-type: none"> • A slow METC approval process will make the industry choose countries that are faster • Shift to less expensive countries with large patient populations • The drug market is growing in the emerging economies • Departure of promising scientists to other countries where they have better opportunities

Recommendations

- Improve international collaboration in order to keep a participating position as a smaller country in the clinical research environment
- Improve political collaboration EZ, so that a link can be made between economic activities with scientific and healthcare activities and the government can create exciting and appealing opportunities for the industry (and consequently for the Dutch research environment)
- Further improve ICH-GCP compliance and awareness of investigators
- Take advantage of the trend that emphasis will shift to the earlier phases in clinical research for cost efficiency reasons, and sell our expertise on translational medicine, predicting pharmacodynamic effects and other early phase research, because this is one of the Netherlands' biggest strengths
- Stimulate further collaboration between industry and academic hospitals
- The government should create a long term vision for establishing and stimulating our knowledge economy

A. Keijzer, MSc and A.G.M. van de Langerijt, MSc (Sanofi-aventis)

8 September 2010, Gouda

Organization: Sanofi-aventis Netherlands B.V.

Description of the Organization: Sanofi-aventis focuses on development, registration, marketing, sales and distribution of prescribed medicines. Sanofi-aventis is the third largest pharmaceutical company in the Netherlands and has approximately 200 employees. Sanofi-aventis is a member of Nefarma and in early 2009 joined as a partner in the Mondriaan project from the Top Institute Pharma (TI Pharma) foundation. In the Netherlands, Sanofi-aventis performs mostly phase II to IV studies, as part of multi-country studies, but also local phase IV studies. The clinical research department of Sanofi-aventis consists of 45 people working solely on clinical research.

Name: Angelique Keijzer, MSc

Title: Clinical Support Manager

Professional background and role in organization: Angelique Keijzer has been working at sanofi-aventis (formerly sanofi-synthelabo) since 1997: first as Clinical Research Associate, then as Clinical Project Manager and since January 2005 as Clinical Support Manager. She is an expert on EUCTD and local legislation, METC approvals, SOPs and training within the department.

Name: Lex van de Langerijt, MSc

Title: Director medical affairs & Clinical operations

Professional background and role in organization: Lex van de Langerijt has been working at Sanofi-aventis since 1994 and is currently Director of Medical Affairs & Clinical Operations and is also head of the Clinical Research Department in the Netherlands.

METC approval process

The CA approval process in the Netherlands is very fast compared to other EU countries (we only have a marginal assessment). The approval process of the METC is on the contrary a hurdle to performing clinical research in the Netherlands. In the experience of Sanofi-aventis, the Netherlands is performing fairly well with respect to the time period between submission and the first patient entering the study. However, before METC approval is obtained for all sites, the Netherlands is often the last in the queue and also frequently comes after the US. There is a visible trend by which METCs and local feasibility committees implement adjusted procedures that are more efficient (smaller committees, separate committees etc.). There is an awareness that they have to be efficient in order to deal with the workload and also to be competitive.

An article (supported by Sanofi-aventis⁷), concerning the vision of local feasibility committees on the local feasibility assessment, has made clear that in their view the problem is not the committee, but instead, the long time taken by the investigator in preparatory work. Sanofi-aventis' suggested solution is to assist the investigator with this preparatory work and to remain on top of the progress of the collection and preparation of the required documents and procedures. This has been shown to be very effective, but only because Sanofi-aventis has been willing to provide the necessary resources.

Effects implementation EU CTD

Initially, the implementation of EU CTD did not really signal an improvement with respect to the METC approval process, due to the fact that local committees did not trust each other's assessment, and consequently an approval for all sites was required anyway (although the idea was to centralize the process and be more efficient). Gradually this situation is improving (see above). The implementation of the EU CTD has resulted in a higher administrative burdens, brought about by the extensive reporting regulations etc. In order to build expertise and consequently be more time efficient Sanofi-aventis established a start-up unit that is focused on submissions and other important start-up activities. Harmonization throughout Europe is not really visible when performing an international trial, since all countries have implemented the directive in a different way (only the minimum requirements are identical). In order to comply with all local requirements, Sanofi-aventis has to bother the investigators with more administration and reporting than is strictly necessary. However, this situation does not have an effect on the competitive position of the Netherlands.

The factors that do have a negative impact on the competitive position of the Netherlands are: the slow local feasibility committees, the more stringent requirements for trials concerning orphan diseases, paediatric trials and gene therapy studies. The approval process at the Central Committee on Research Involving Human Subjects (CCMO) for gene therapy studies is troublesome and in addition there is a legal obligation requiring the presence of safety officers in the hospital. An example of this troublesome process occurred during a study initiated by Sanofi-aventis. Whereas all other countries involved did not classify the product studied as a genetically modified organism, the Netherlands did and as such it was subject to CCMO approval. This approval process lasted a year and with the trial eventually being rejected. Sanofi-aventis visited the CCMO to clarify the failures in the process and established that there was not enough progress surveillance and also that the management infrastructure was not of

⁷ Martine van Duijn, student BioPharmaceutical Sciences Universiteit Leiden and trainee at sanofi-aventis the Netherlands BV; Edit leijendekker, Country Research Manager, Astellas Pharma BV (Draft)version 15 June 2010 – “Toetsing van de lokale uitvoerbaarheid; de visie van toetsingscommissies”

a sufficiently professional level (e.g. the CCMO was not reachable for a period of 3 months during the above process). Sanofi-aventis is confident that the CCMO will not let this happen again. However, the requirement for assigning safety officers in the hospital is not very attractive from a cost perspective, especially if actual patient recruitment is not certain.

When obtaining a request from the head office, Lex van de Langerijt now rejects this type of study immediately. This development is of course a threat to this type of research occurring in the Netherlands, and it is pre-eminently an area of research where the Dutch can play an important role. Because of the very technical and scientific level of this kind of research, there is high interest in performing these trials in the Netherlands. This is confirmed by the fact that, when Lex van de Langerijt rejects this type of study, the head office of Sanofi-aventis will attempt to find alternative circumstances in which to perform the trial in the Netherlands (although for other studies it is very difficult to get on the list in the Netherlands).

Standardization of clinical trial documents

METCs are indicating that they will benefit from standardized patient informed consent forms and clinical trial agreements and Nefarma is working on both. The CCMO has initiated a standard clinical trial agreement based on the UK NHS Trust Hospitals template and Nefarma is now fine-tuning the template with the involvement of parties like the NFU, STZ, NVZ, NVMETC, ACRON and the CCMO. The requirement from the CCMO that signed agreement must be submitted before approval causes delays and other issues: sometimes the budget is not even approved by the head office of Sanofi-aventis at the time of submission.

The quality of clinical research in the Netherlands

The Netherlands is known for its qualified investigators and the technical experience and knowledge required to perform the most complicated clinical trials. In addition there are some very good research networks that facilitate patient recruitment for certain therapeutic areas (see below).

Costs

Cost efficiency has become more important when selecting a country in which to conduct the clinical trial, since nowadays the execution of the more straightforward studies can also be done in other (less costly) countries: the quality in countries like India and in Eastern Europe is also very good.

Recruitment and motivation of investigators

The recruitment and motivation of investigators depends mainly upon the therapeutic area or the product. It is easier to recruit investigators for a new first in class product than for a

product that is the fourth in row. If the drug is not very interesting, the investigator will only be attracted if the investigator fee is substantial, but even then motivated investigators are hard to find.

Training and education investigators

The problem in the Netherlands, is that there is no central registration of ICH-GCP trained investigators. To date only BROK-course participants are registered. Furthermore, pharmaceutical companies do not accept each other's ICH-GCP courses which is very inefficient. Seemingly, there is a lack of trust in the quality of the other party. Most pharmaceutical companies will accept a registration, if the investigator did the ICH-GCP training at the company concerned or from an accredited institute (like the BROK-course). However, it is difficult to define an accredited institute and efforts to set up a central institution for exams and registration acknowledged as such by all stakeholders (e.g. by Mediavision and the Foundation "Certificering Klinisch Wetenschappelijk Onderzoeker" (see www.ckwo.org)) were not successful.

The most efficient method would involve all investigators being obliged to receive ICH-GCP training at an accredited institute. The successful participants would be registered centrally and follow a refresh-course every few years. This would also solve the issue that the Principal Investigator is usually not interested in doing the course and sends the research teams to the investigator meetings (where ICH-GCP training is provided). This is not difficult to arrange and would contribute enormously to the improvement of the clinical research climate in the Netherlands. It would also be helpful if the course was part of the training curriculum for investigators or medical schools.

Infrastructure hospitals

Research desks are very helpful in supporting clinical trial activities within hospitals. However, they often function per department and are mainly focused on contractual activities instead of the communication between the laboratory and the pharmacy. The laboratory and the pharmacy often wish to have a separate agreement with the sponsor, because of budget reasons. It would be advisable if a hospital would set-up a pool of nurses that could be used throughout the departments in an efficient manner and facilitate good quality collaboration with the pharmacy and the laboratory.

Sanofi-aventis is working on an initiative called *Research Proof*. This initiative has been set-up to support hospitals in identifying bottlenecks when performing a clinical trial and to obtain good insight into: their research management, to create harmonization and lastly to create the opportunity to learn from other hospitals. The results of the assessment can then be discussed

with the hospital board. In this way an effective measure scan can be taken to improve the clinical research process in hospitals.

Recruitment of study subjects

The clinical trial industry is usually portrayed in the media and by the government in a very negative way. This perception also influences the decision by patient to participate in a study and consequently might lead to discouragement of the investigators (because of slow patient recruitment). Nefarma is trying to improve the image of the industry by way of informative leaflets etc.

The relationship with their treating physician is however usually the most decisive factor in a patients decision to participate. Therefore, these relationships are crucial for the success of a clinical trial. It also helps that the Netherlands has an excellent infrastructure and good networks like the WCN and VCRN (cardiovascular network). The local Sanofi-aventis research unit can bring large cardiovascular studies to the Netherlands due to this type of network. Access to patients is more important to a pharmaceutical company than costs.

However, Diabetes research has become more complicated in the Netherlands owing largely to a shift to the first line of care, and the lack of interest among general practitioners to participate in a clinical trial. This makes it more difficult to get diabetes trials to the Netherlands, since in other countries the diabetes patients remain with the specialists. Sanofi-aventis has invested for years in the motivation of the care groups and GPs, which has proven to be a difficult task. Another down-side is that the patients are spread in small amounts over the GP practices and therefore recruitment is slower. GPs are also often not sufficiently equipped to participate in clinical trials.

Sanofi-aventis uses a very strict and thorough selection procedure to ensure that a site is motivated, well prepared and able to recruit the estimated number of patients. If a study is initiated by the head office, the local Sanofi-aventis office has to work through an extensive feasibility questionnaire to, amongst other things, assess the recruitment potential, with only a 5% chance that the Netherlands is selected.

Access to well-trained CRO staff

Sanofi-aventis conducts most of its clinical research internally. Only where big international studies are involved, for which the resources are not in house, will CROs get involved. This decision is made at a corporate level and the CRO contracted is always an international one. Sanofi-aventis has had good and bad experiences with CROs. Sometimes the conduct of a clinical trial is also difficult for the CRO, due to restrictions initiated by the client.

Trends in clinical research

The current trends in clinical research are:

1. trials with small indications, development of specific innovative drugs
2. personalized medicine, medicine developed for genetic subsets
3. antibiotics research (because of the resistance that is developed for existing antibiotics)
4. ageing diseases
5. paediatric trials

Following the introduction of the Medicines for Children Research Network (MCRN), 2 years ago, the Netherlands has the potential to take a leading position. The MCRN unfortunately has not yet received enough projects, and is bound by the stringent regulations found in the Netherlands (compared to other EU countries). For example, when parents of children with Duchenne collected money for research, the research could not be performed in the Netherlands because of stringent regulation. Therefore it was decided to conduct the trial in other EU countries. In the opinion of Angelique Keijzer and Lex van de Langerijt, paediatric trials are the future and it is a real opportunity for the Dutch clinical research arena to excel in this type of trial.

The effects of globalization

Due to the low costs and also the large number of available naïve patients, industry is shifting to the emerging markets. Asthma and diabetes studies are not performed in the Netherlands by Sanofi-aventis due to the difficulty in finding and recruiting naïve patients. Russia has a long start-up period, but this is now standard because of their fast patient recruitment. Europe will never be completely ignored, because companies will often want to submit to the EMA which requires different genetic populations. The danger remains that due to cost efficiencies the sponsors will choose bigger countries in Europe that can deliver more patients (e.g. UK, France and Germany). Due to its size, the difficulty faced in getting the compound on the reimbursement list and the reluctance to prescribe new medicine, the Netherlands is not seen as very appealing in future market potential.

The role of the Dutch government

It is a troubling development, that R&D units of large pharmaceutical companies are leaving the Netherlands. In the case of Organon (MSD) the Dutch government has chosen to apply the free market principle, although it seems that Sarkozy was able to save the MSD units in France by communicating directly with the CEO of MSD. This attitude is not in line with the innovation platform and the desire for a knowledge based economy. The government also fails to show enough long term vision in this area (see TIPharma).

SWOT Analysis

<p>Strengths</p> <ul style="list-style-type: none"> • Qualified investigators and study teams • Well-equipped to handle more technical studies 	<p>Weaknesses</p> <ul style="list-style-type: none"> • Slow local feasibility process and therefore slow METC approval process • Inefficient ICH-GCP recognition infrastructure and lack of a mandatory training and central register • Lack of a good and central research structure in hospitals
<p>Opportunities</p> <ul style="list-style-type: none"> • Adjust the requirements for orphan disease, paediatrics and gene therapy trial to the requirements in other countries in the EU (now our laws are more stringent), so that the Dutch clinical research environment can benefit from the fact that this type of studies is pre-eminently interesting for their more unique technical knowledge and experience • Further strengthen MCRN network and draw international attention in order to increase the number of projects so that we can build experience • Arrange for centralized registration and the obligation to follow ICH-GCP training at an accredited institute. Assign a few of these institutes. • Create initiatives that can improve the clinical research structure at the hospital and create awareness with the hospital boards 	<p>Threats</p> <ul style="list-style-type: none"> • Stringent regulations for gene therapy and paediatric studies are a missed opportunity for the Dutch technical research environment

Recommendations

- Adjust the requirements for orphan disease, paediatrics and gene therapy trials to mirror those requirements in other EU countries (now our laws are more stringent), so that the Dutch clinical research environment can benefit from the fact that this type of studies is pre-eminently interesting for it's more unique technical knowledge and experience
- Further strengthen the MCRN network and draw international attention in order to increase the number of projects so that we can build experience
- Arrange for centralized registration and the obligation to follow ICH-GCP training at an accredited institute. Assign this to several institutes.
- Create initiatives that can improve the clinical research structure at hospitals and create awareness on hospital boards
- Streamline the mind-set of METCs, industry, investigators, hospital boards, patients and government to build a stronger research climate in the Netherlands

J. Rijniere, MD (Amgen)

23 September 2010, Breda

Name: Joep Rijniere, MD

Organization: Amgen BV

Title: Medical Director

Description of the Organization: Amgen BV is a Biotech company focused on clinical research, marketing and sales. Their special indication areas are oncology, kidney disease and rheumatoid arthritis. Amgen BV is participating in international multi-centre phase II to IV trials.

Professional background and role in organization: Joep Rijniere has been working in the clinical trial industry for 23 years. He has worked in a number of different roles, including: Medical Advisor, at Ciba-Geigy, was International Clinical Research Operations Manager at Novartis, Medical Director at Pharmacia (& Upjohn) (later acquired by Pfizer), Manager Corporate Affairs at Pfizer, Global Medical Director Neurology at Serono, Medical Director the Netherlands at Schering-Plough and since August 2009 he works as Medical Director at Amgen BV. For the last 3 years, Joep Rijniere has been actively involved in a working group from Nefarma aiming to improve the Research and Development climate in the Netherlands, and for which he elaborated on the laws and regulations in the Netherlands and the infrastructure in the hospitals. The vision with some recommendations and standpoints from Nefarma will be made public in the near future.

METC approval process

The METC approval process in the Netherlands is slow. Academic centres attempt to undermine each other and do not trust each other's assessments and opinions, resulting in substantial delays to the approval process. A "Locale Uitvoerbaarheids Toetsing (LUT)" is very often done by a METC which does not restrict itself to doing the LUT, but again performs an ethical review. In the case of competitive recruitment, delays to the approval process result in a situation where the Dutch sites are opened when all patients have already been included in the trial process and other countries have already finished their trial. The METCs of universities should take a united stance as some academic centre already did and not redo an ethical approval. If the Netherlands would like to remain competitive with other countries then it must be acknowledged that it is too small a country to have different opinions in eight different centres. Discussion and debate on smaller issues must of course be allowed, but this should be kept out of the approval process.

Delays affecting the trial process are not caused by a lack of rules and regulations or a failure to collaborate between investigators, but by the separate assessments of the local feasibility committees. The difficulty here is that the only entity authorized to correct and instruct the committees is the hospital board, and clinical research is usually not on its agenda. The CCMO and the Dutch Society of Ethics Committees (NVMETC) do not possess the authorization and the tools to correct and exert pressure on the committee. Positive exception are the METC and local feasibility committee in the Erasmus MC in Rotterdam and the Leiden University Medical Centre: they have constructed a very efficient process and understand that this makes them competitive. The infrastructure of a hospital is in this perspective extremely important, because it creates the basis for clinical research in the hospital and provides a voice to the hospital board.

Effects implementation EU CTD

The implementation of the EU CTD brought with it additional administrative burdens. However the other EU countries are dealing with those issues as well, and as such it does not have an effect on the Netherlands' competitive position, except for implementation of the CA/METC review. Bureaucracy in the Netherlands remains less than that in the US, but diligent monitoring will be required in order to maintain the status quo and continue to enjoy this more favourable position.

Standardization of clinical trial documents

Nefarma is working on the standardization of patient information and the clinical trial agreement. Nefarma is collaborating with the CCMO, hospitals and other parties on a standard contract template and is now consulting different parties (such as the ACRON, NFU, NVZ) to produce a document with a solid basis. All players in clinical research are content with the development of a standard template. At the moment site agreement negotiations can be very time consuming.

The quality of clinical research in the Netherlands

The infrastructure in place for clinical research and development in the Netherlands is in principle very good. In some areas it has the status of an internationally leading player. In order to remain competitive, further improvements in those areas is required. Additionally, the Netherlands should be very selective in exploring and developing new areas of expertise. A threat exists that other countries are developing too and in the meantime are often also in possession of high quality equipment and facilities. The Netherlands continues to house many Global Key Opinion Leaders (GKOL), and it is important to keep them in the country and give them the means to continue to be involved in R&D: at the moment research and development is moving away from the Netherlands, this will result in less publications and a down-wards

spiral may follow. Currently, the Netherlands remains competitive in phase II early stage research, complex research and Phase I research (also in oncology) and in selective later phase research areas (e.g. cardiology, pulmonology, etc.) often done with Coop-groups.

Costs

The Netherlands is an expensive country when compared to other countries in Europe. In the experience of Joep Rijnierse costs in the Netherlands are increasing. In addition to the very generous investigator fee that is paid by pharmaceutical companies, hospitals often wish to be reimbursed for overhead costs (sometimes as high as 16%) where one can wonder what this is for since the procedures, METC, pharmacy, investigators, etc. are already paid for in full (including overhead fee). The Netherlands does not have an interesting and appealing market potential and if also more expensive than other countries, it will prove extremely difficult to attract research and development to the Netherlands. The environment in the Netherlands cannot and should not be compared to countries such as India or China with very low costs, but it is important to remain competitive to comparable Western-European countries.

Recruitment and motivation of investigators

The Netherlands is particularly research-minded and hospital staff are aware that clinical research improves patient health care and also quality of regular care. Investigators are interested in studies where they can provide input into the protocol and have an opportunity to publish. It is more difficult to motivate investigators to participate in late phase international studies. Generating studies with general practitioners has become more difficult. Reasons for this decline include feminization (more part-time GPs), the lack traditionally of participation in clinical research and also the high workload of GPs. Some level of cooperation has established good infrastructure for research, and these initiatives can be supported by industry. Also cooperative groups in other areas have proven to work well and attracted research to The Netherlands.

Training and education investigators

The hospital staff are usually well-trained. If the research is performed by medical doctors in training or when staff frequently changes, it is difficult to provide the same level of training in a hospital as if it was dedicated research staff. A good infrastructure in the hospital facilitates ICH-GCP training. Some investigators have been careless regarding ICH-GCP training requirement, but the industry has also been extreme in their un-willingness to acknowledge training certificates from other sponsors. It would be beneficial to have certified training in the Netherlands, so that besides a company's own training regime, the certified training would also be accepted. The BROK-course is a good initiative but very detailed and bureaucratic, which is appropriate for the academies, but for the other hospitals it would be advantageous

to also create a more practical version. Electronic training and exams can be very effective and efficient. This should also be the solution to the problem that, investigators often do not attend the investigator meeting (where an ICH-GCP training is provided) themselves.

Infrastructure hospitals

Research desks at hospitals can be useful if they facilitate and support the investigator with respect to resources and knowledge, and the department pays for the services used. A situation where it is mandatory to perform all research in the hospital through a central research desk would not work well: it will become bureaucratic, investigators will not be happy with the fact that they cannot negotiate directly with the sponsor and the sponsors will not be happy with the overhead costs associated with such a trial desk. There is a big difference in the infrastructure for clinical research between different departments. A considerable number of investigators are for example performing investigator initiated trials with the infrastructure and income generated from industry sponsored research (e.g. most academic centres and some STZ hospitals like Kennemerland).

Recruitment of study subjects

In general patients are still willing to participate in clinical trials. Specialist are usually better equipped to explain to the patient why they should participate than general practitioners. Also they have often a bigger patient pool with a specific profile needed for a specific trial than GPs do and therefore their recruitment rates are usually higher.

Collaboration industry, CROs and academic hospitals

The industry is very interested in collaboration with academic hospitals. It does however prove difficult to generate support from the head office of a pharmaceutical company for participation in TI-Pharma projects because of the intent that TI-Pharma projects should be projects before competition. For some interactions with academia intellectual property arrangements can be very important for the industry and cause some discussions.

Trends in clinical research

The initiative of the Medicines for Children Research Network (MCRN) which profiles the Netherlands as a country for paediatric research is very inspiring, but not yet very successful. The problem with this initiative lies in the fact that the network is current, but has not enough yet garnered enough experience with regard to paediatric research. Sponsors are therefore relatively cautious when it comes to conducting such a trial in the Netherlands (leading again to no experience being built). The stringent regulations for this type of study are not helping either.

The effects of globalization

The closure of the Research unit from Organon (MSD) is not surprising when looking at the management of large international company. When activities of one of the research units worldwide, like the former Organon Research within MSD, are not fitting the research direction a company wants to go or are, compared to other units, maybe not top-of the bill or creating cutting-edge technology, a logical decision for such a company is to close down such a unit, when costs have to be cut. The impact on the clinical research environment in the Netherlands however, is underestimated: it is not simply the loss of jobs; but also the loss of existing relationships and joint ventures with the academies (e.g. TlPharma) and the missed opportunity of obtaining knowledge from students and talented scientists that will move abroad. The research activities of other pharmaceutical companies can still be saved for the Netherlands (e.g. by way of stimulating start-ups). Clinical development is another story. Although the Netherlands has already lost some of these activities to other countries and regions they still are competitive. The challenge here is to remain competitive wherever possible. Both Research and Development activities fit with the strategy of the Dutch government to become “Nederland Kennisland” and thus should have full attention which is not always the case.

The role of the Dutch government

Politicians are not being supportive of the industry in the media. There is limited consistent and close collaboration between the departments of VWS and EZ.

Is the Netherlands an attractive good country to establish your company

It is very difficult to get a compound on the list of reimbursed compounds in the Netherlands and the process takes far too long. The image of the industry is worse than anywhere else in the World. If the government provided incentives to industry to stimulate research and development in the Netherlands, it would create a more appealing environment for a company to settle in (see for example, the situation in Switzerland).

SWOT Analysis

Strengths <ul style="list-style-type: none">• Excellent phase I setting• Good in early stage, complex trials• Good functioning Coop-groups in certain areas• Good well respected GKOL network with high international impact• High number of spin-off and start-up companies	Weaknesses <ul style="list-style-type: none">• Slow METC/LUT approval process• More stringent regulations than other European countries for some study types• Costs are high compared to other EU countries• No constant quality in all departments in academia and research oriented hospitals
Opportunities <ul style="list-style-type: none">• Stimulate performance of interesting clinical trials by establishing a good infrastructure (financial incentives)• Stimulate more collaboration between the eight academic centres and also with the top clinics• Improvement of cooperation with industry as a trustworthy partner (stop only emphasizing negative image)• Improve infrastructure for R&D in academia and peripheral hospitals• More participation of the patient organizations• Standardization of CTA and PIF to improve approval times	Threats <ul style="list-style-type: none">• More bureaucracy with too much workload• Loss of Global Key Opinion Leaders and less involvement in global R&D• Catch up of quality R&D activities by other countries• More trials allocated to CEE and BRIC countries• Loss of leading position with global impact (Leading KOLs, high impact publication, leading universities, etc.)

Recommendations

- Further improve the infrastructure for R&D in centres, but also in The Netherlands as a whole
- Turn around the slow METC/LUT approval process (e.g. Improve LUT, standard CTA and PIF)
- Ensure that rules and regulations do not obstruct clinical research and implement in such a way that NL becomes competitive again
- Ensure that global KOLs will not leave the country and stay closely engaged in global R&D
- Create awareness within hospital boards about the importance of R&D
- Wherever possible create collaboratively in research networks within or across centres (Trial groups, cooperative groups, specialized network groups, etc.)
- Create collaboration where industry is seen as a trustworthy partner
- Provide financial incentives or other stimulants to the industry in order to strengthen the Dutch clinical trial environment

