7 Appendices

Concrete proposals from the four workshop sessions regarding research and technology projects are listed in 7.1 appendix 1. Although 3 years have past since the first NSMF workshop, the projects listed in the first report are still of value today, cf. www.eufeps.org. The list of participants and workshop programme are attached as 7.2 and 7.3 appendix 2 and 3, respectively. Finally, 7.4 appendix 4 contains the executive summary of "New Safe Medicines Faster. A new concept for drug development„ by Jørgen Dirach.

7.1 Appendix 1: Research and technology projects

7.1.1 New technologies for drug development

At this workshop, the focus was on techniques. That means the discussions covered a wide range of challenges encountered by the pharmaceutical scientists involved in the drug development process. For this reason, workshop participants tried to identify technological hurdles during the drug development process. A number of the issues in this section are also mentioned in sections 7.2-7.4, where the emphasis is on conceptual importance rather than technological implications.

7.1.1.1 Identification of topics

Four major research fields were identified as the priorities for obtaining a faster and more effective drug development process. They include:

- Fast and reliable drug selection approaches
- Advanced drug delivery and targeting technologies
- Advanced pharmaceutical technology and processing
- New approaches for optimised individual drug therapy

Before the more detailed discussion, some general observations and remarks should be made:

New technological developments should be open to both new and generic drugs. Diseases announced in the first two rounds of FP6 could serve as vehicles for the projects, although broader disease groups would be preferable (e.g. chronic inflammatory diseases, ageing, paediatric drug development) in order to establish different working groups in a more broadly defined project.

Closer interaction between the regulatory authorities and other stakeholders is of critical importance. This includes discussions about the value of and need for new technologies and approaches at an early stage of their development. To this end, a much more proactive European regulatory body is highly desirable. The regulatory authorities should consider, evaluate and regulate emerging technologies, for example by using public funds to initiate regulatory-academic-industry platforms on emerging topics and technologies. This could be done through a research and development arm of the EMEA. In this respect, the current strategy of the US Federal Drug Agency (FDA) is regarded as a sort of role model.

7.1.1.2 Research and technology projects

(i) Fast and reliable drug selection approaches

To screen and select the best from a library of drug candidates, the following major hurdles have been identified and should be addressed to optimise the attrition process in the early stages of development:

- Assess the 'drugability' of the candidate molecule.
On the basis of the molecular structure, can we predict whether a candidate drug is likely to pass successfully through the 'drug pipeline'? Algorithms are under way but need further refinement.

- Assess early toxicity and ADME properties of the candidate drug.
The challenge is to develop reliable *in vitro* alternative approaches for animal work related to absorption, distribution, metabolism and excretion parameters (ADME). In this connection, the use of new genetic information is important. There is also a need to improve the performance of early stage toxicity tests as the high throughput screening (HTS) programmes turn out massive numbers of candidate drug molecules. Validated approaches that further limit the use of animals in the drug development process should be stimulated in parallel.

- Assess bioavailability/availability at the target site.
The new generations of candidate drug molecules are either identified through HTS selection from combinatorial libraries or biotechnological sources. Combinatorial, chemistry-derived compounds tend to have poor bioavailability due to their poor water-solubility and/or stability characteristics (e.g. active excretion pump systems and cytochrom P450 substrates). Biotechnology products are (glyco-)proteins and are administered intravenously. They would, however, be much more patient-friendly if non-parenteral administration routes became available.

- Find proper biomarkers (surrogate markers).
Monitoring biomarkers may help to speed up the drug selection process. At present, there is a great need to validate approaches using biomarkers in early drug development and surrogate endpoints in clinical trials (see also 7.3.2).

- Improve models predicting animal to human behaviour (animal scaling).
The use of animals in the development of new medicines is of critical importance. However, attempts to minimise their use on the basis of new scientific insights should be encouraged.

- Develop new bioanalytical tools for monitoring the fate of drugs.
Micro-dosing and N-in-one cassette tests require highly sensitive, selective and quantitative analytical techniques. Examples of strategies that may help to meet these challenges are, for instance, based on positron emission tomography (PET) or advanced mass spectroscopic (MS) techniques. In addition, there is a great need for non-invasive imaging techniques to monitor the fate of a candidate drug in vivo.

Pay attention to 'system biology' approaches (from *in vitro* to full animal).
Scientists, such as molecular biologists, cell biologists, physico-chemists, biochemists, pathologists, toxicologists, ADME experts, informatics experts and

pharmaceutical technologists, who used to work separately on the development of novel drugs, should be encouraged to set up 'concerted actions'.

(ii) Advanced drug delivery and targeting technologies
Drug delivery and drug targeting include the development of new delivery systems to maximize the drug's opportunities to access the therapeutic target site, new biocompatible materials, homing devices, intracellular transport devices for target cell/site selection, target cell entry, endosomal escape, nuclear transport and nuclear import.

It is of utmost importance that the right drug is delivered in the right dose at the right time via the right route of administration to the right part of the body of the right patient. Many highly promising drug candidates have been rejected because of poor bioavailability or blocked access to the target site. This applies to the new generation of library-based 'small' molecules, which suffer from poor bioavailability (see above), and even more so to biotech products ((glyco)proteins) or DNA (derivatives). These large molecules cannot pass membranes and need carrier systems, preferably with homing devices for target selectivity, i.e. for finding the target cell/site and intracellular transport. These complex, nanometer-size, often self-assembling systems should, of course, also be non-immunogenic.

(iii) Advanced pharmaceutical technology and processing
Pharmaceutical technology is seen by many as an old, rather stagnant field. Research money is difficult to obtain for new developments and, therefore, many academic top groups choose to avoid the field altogether. But, in reality, there are many challenges still to be met. The group identified the following fields where a new élan is highly desirable.

- Support solid state/particle engineering.
The physical form of a drug or excipient is often of critical importance to its performance during manufacturing and storage and when administered to the patient. For this reason, crystal engineering has gained renewed attention in the pharmaceutical world, attention that should be further expanded.

- Improve bioavailability.
The oral bioavailability of many drugs is low and varying, exposing the patient to too low or highly varying doses of the drug. Parenteral administration is not a patient-friendly alternative. Bio-enhancers based on different and newly discovered working mechanisms should be further evaluated (for example, bio-adhesives, co-substrates, stabilisers and other routes of administration).

- Establish basic insights in *in vivo –in vitro* correlations.
Animal and clinical tests are regularly performed to ensure product quality when producing pharmaceuticals. This is the case for drugs such as therapeutic proteins or vaccines which are difficult to characterise fully by analytical means. These tests are often also necessary after the modification of existing pharmaceutical formulations. Basic work on identifying *in vitro-in vivo* correlations is highly necessary.

- Support basic work on drug substance and scale-up.
Scaling-up problems often determine the development rate of a drug. Academic

groups don't have the means to perform basic work in this area due to the high cost of equipment and materials. A strategy is required for working on basic aspects of up-scaling in the pharmaceutical industry.

- Do not forget the analytical tools.

All the issues mentioned here depend heavily on sensitive, specific and reliable analytical approaches. For instance, HTS strategies require automated systems in miniaturised form. This implies that attention should be paid to robotics and miniaturisation processes. There is also a growing demand for monitoring the production process right the way through. For this reason, non-invasive detection technologies are in high demand.

(iv) New approaches to optimise individual drug therapy
Personalised medicine is a trend that is expected to develop in the years to come. The possibilities for existing drugs include the application of personal dosing and scheduling schemes. New drugs for mono as well as multi-genetic and environmentally affected disorders will also be developed. Such drugs may target specific sub-types of a disease such as diabetes, asthma, depression and Parkinson's disease. Their selection will be based on new diagnostic tests, responder tests for efficacy and tests for safety risks and kinetic and metabolic properties. To develop these tests, better insight is required into the etiology and pathophysiology of the disorder and the mode of action of the pharmaceutical products. A prerequisite of this is the development of new diagnostic tools in the form of, for instance, array technologies and validated biomarkers and endpoint markers. Sensors embedded for drug response monitoring are also needed.

7.1.2 Modelling and simulation in drug development

Major areas of application include the creation of virtual human populations that typify variations in human absorption, distribution, metabolism and excretion of drugs. Other areas are pharmacodynamics, models of complex systems, and modelling of diseases and disease progression.

In addition to the models themselves, it is necessary to generate basic knowledge about the essential model components. This requires the creation of component libraries that will inform the regulatory authorities about the application. The functional relationships between the components found in human populations, as well as variables such as genetics, age, sex, gender and disease, should also be established.

The creation of generic rules is possible and highly desirable for pharmacokinetic modelling as pharmacokinetics is generic and applies to most "small,, drug molecules. Furthermore, pharmacodynamic modelling is much more disease and target-dependent, making it possible to design criteria as a part of model validation.

Such research is pre-competitive and beneficial for many companies. For this reason, public funding is required to ensure the generation of publicly accessible data. In this context, it should be emphasised that modelling is a powerful organiser and accumulator of knowledge and, together with simulation, provides excellent learning tools.

Concrete proposals for projects include:

(i) Virtual pharmacokinetic (PK) model

The integration of ADME modelling and simulation throughout the drug discovery and development process is the ultimate goal. One prerequisite is to build a "virtual individual,, and "virtual populations,, by collecting, producing (if needed) and putting together a large bank of biochemical, biological, genomic, physiological and demographic data, and making sure that it is reliable. For example, there is a need for physiological data as a function of age (modelling in paediatric pharmacology). A model (or models) of drug handling could be built on the basis of the above databank, starting with model components. Other projects, which could provide examples and advice, are COST B15: Modelling During Drug Development, and SIMCYP, where software is being developed to predict, using *in vitro* data, the likely range of intensity of drug-drug interactions when patients take two or more drugs.

(ii) Pharmacodynamic (PD) modelling

The primary objective of pharmacodynamic modelling is to characterise and predict drug effects *in vivo* in healthy and disease conditions. PD modelling should optimally be linked to PK modelling to provide the time dimension in drug effects and behaviour. A key factor in the application of PK/PD modelling is the incorporation of information about important rate-limiting processes at the level of pharmacokinetics (biotransformation, transport), pharmacodynamics (receptors, transducers, signal transduction) or homeostatic control mechanisms (tolerance). Mechanism-based PK/PD models are particularly valuable for extrapolation and prediction. Mechanism-based models are expected to be useful for extrapolation from *in vitro* receptor test systems to the *in vivo* situation, prediction of tissue selectivity of drug effects, extrapolation from animal investigations to humans, as well as understanding and predicting variations in drug response.

PK/PD modelling may also provide the scientific basis for the design of new drug molecules, the selection of drug candidates, the optimisation of the dosing and delivery profile of a drug, and the evaluation of drug effects in clinical trials.

(iii) Complex systems modelling

This relates to *in silico* modelling and biosimulation of cell function, organ and system physiology in health and disease metabonomics.

(iv) Disease modelling

The modelling of diseases and disease progression is currently the subject of great interest, primarily because the application of modelling may either lead to a reduction in the number of patients enrolled for clinical trials or better characterisation and stratification of the population required for such trials. This type of modelling should be based on a mechanistic understanding of the disease process as a function of time and not merely on individual potential target molecules, i.e. systems simulation vs. target simulation. Consequently, there is a need to characterise disease progression, since this may lead to an overall reduction in the number and duration of clinical trials. To date, only a few attempts have been made to explore mechanistic modelling of disease progression.

(v) Molecular modelling in relation to pharmacogenomics

This concerns polymorphisms of all proteins involved in PK(ADME)/PD, e.g. cytochrome P oxidases (CYPs), receptors, and transporters. Two main scientific approaches have been made to *in silico* prediction of drug metabolism and drug action. The first is based on the physicochemical properties of the molecule itself, often utilising structure-activity relationships. The second is based on knowledge of the structure of the enzyme or the receptor and/or their mechanisms of action. Most recently, approaches have been developed that incorporate aspects of both. The second approach will clearly yield tools for predicting *in silico* changes in the structure and function of polymorphic proteins.

To secure the general availability of both the models created and the library of components, a pan-European website should be established for general use, preferably based on a centralised system. Problems with intellectual property rights are, though, foreseen and must be handled upfront.

Regarding training and education, it will be necessary to educate regulators to improve their receptiveness towards modelling as a tool. For SMEs, problems are anticipated with web-based models as the companies will still lack the expertise to put such models to optimum use. This suggests that there may be room for innovative contract-based services.

7.1.3 Challenges and issues in shortening the time of clinical development, including better characterisation of patients for drug development

The third discussion session focused on the clinical drug development and the involved patients.

7.1.3.1 Rethinking drug development

(i) Where are the barriers to further clinical drug development?

The chronic disease area is in the greatest need of improvement and also represents the greatest burden to the community. Cancer, cardio-vascular and rheumatic diseases, diabetes and neuro-psychiatric disorders are among the diseases in this category[3]. The current clinical development process is too long and too expensive to be effective in developing really innovative medicines. This is evident from the decline in the number of newly registered innovative medicines, despite increasing investments in drug development[4].

(ii) Knowledge generation as the basis for effective development

Traditional drug development rests upon the notion that finding the chemical substance is difficult, but that, once found, the treatment of the disease is quite straightforward. This was true for, for example, antibiotics and hypertension where the biology of the disease is approachable, but it does not apply to many of the diseases mentioned above where the biology is still largely unclear or affects many organs. These are some of the diseases that will generate the biggest medical need in the years ahead.

[3] http://www.who.int/hpr/archive/expo/futures06.html
[4] Van den Haak MA, Vounatsos FJG, McAuslane JAN. (2002) International pharmaceutical R&D Expenditure and Sales 2001. Pharmaceutical Investment and Output Survey 2001: Data report 1. CMR International Report, CMR02-171RA

Due to the complexity of the diseases that need to be tackled pathophysiologically, directed therapies are still rare for these conditions. But they are likely to be the only way forward. Greater knowledge about disease mechanisms and a better understanding of disease/patient heterogeneity is, therefore, a necessity. The generation of clinically relevant biomarkers is a pressing demand; in many cases, they are still lacking. Finding markers that indicate disease severity and responsiveness to specific and effective treatment is best achieved by gaining a thorough understanding of the disease. Adequate and validated biomarkers would decrease the size of clinical trials and even the whole clinical development programme, providing they are used in normal clinical practice. This will be of major benefit to the patients who will receive the right treatment at the right dose from the outset. Many of the chronic diseases mentioned above could be made subjects of a concerted European initiative. The most rewarding areas with the greatest medical need and the highest chances of success should be identified for public support.

(iii) Science is not enough; improvement of the process is needed

Any platform for effective development is critically dependent upon patient collaboration, which should be addressed in a pan-European effort since attitudes towards participation in clinical trials vary widely throughout Europe. More efficacious, academic investigator mediated, clinical trials are set back due to:

- the drug companies' domination of process infrastructure
- the EU directive requirement that academic clinical drug research observes the Good Clinical Practice (GCP) ethical and quality system
- the cost of current commercial computer systems, which are too expensive for academic research and not sufficiently integrated with health care information systems
- the lack of integration between IT systems and EMEA systems

The establishment of the EU GCP directive on clinical trials[5] is a major step towards harmonising the rules for clinical research in Europe. Now there is also an opportunity to harmonise the underlying processes, which are currently superimposed on individual researchers by pharmaceutical companies which are only interested in their own trials. This leads to expensive system duplication and confusing situations for investigators working with systems from more than one company. If some of the processes could be harmonised among clinical researchers, many opportunities for important clinical research could be tackled without the help of industry. At the same time, performing trials in collaboration with industry would be standardised and, thereby, cheaper and more effective. In time, this will have a downstream effect on drug pricing and availability to European patients. The academic initiative, ECRIN[6] which aims to create national network centres for the implementation of European standards and clinical research training, has just applied for FP6 support.

(iv) Patient recruitment and data management

These two distinct areas in particular call for a concerted effort.

Patient selection/recruitment frequently limits the rate of drug development. Following the EU Good Clinical Practice directive, patients are assured an ethical,

[5] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001
[6] ECRIN: European Clinical Research Infrastructures Network

safe and harmonised approach to trials. An EU information campaign is sorely needed with a similar look and feel, to emphasise both the safety of trials and the importance of participating for the benefit of health care. Such a campaign could be a joint financial effort between industry and governments but should be spearheaded by governments. This could also lead to a pan-European website where patients could be matched to trials. If companies paid a fee for placing their research on the website, this money could pay for the academic researcher who wants to do the same. More effective post-marketing surveillance could also decrease the size of safety databases when drug dossiers are submitted for approval, thus transferring the cost from the developer to the public sector.

An improved IT infrastructure and open systems for data management and a clinical research toolbox are further needed. Data management has an obvious need for open systems. The lack of a proper IT infrastructure will perhaps be the greatest drawback for hospitals and universities in adopting Good Clinical Practices in their academic studies. In fact, this is just as much of a problem for drug companies that still have to arrange an IT infrastructure for every study they do. A pan-European IT infrastructure for clinical trial data management is technically within reach. If standards can be established and adopted, this may eventually lead to large reductions in overhead costs for industry and a great expansion of the possibilities for academics to study health care interventions in pan-European collaboration. This will considerably improve the competitive position of Europe versus the US and Japan.

A trial computer toolbox for clinical researchers would be beneficial for European clinical research as it would guarantee independence, provide opportunities for disseminating technology throughout the EU, and ensure the rapid availability of safety and efficacy data both during and after more effective, post-marketing surveillance.

7.1.3.2 Research and technology projects

Specific project proposals include:

(i) Development of an integrated patient information and recruitment system in Europe

This concerns an integrated European database with built-in security and confidentiality. Such a system would avoid limitations on patients through unnecessary competition. Regarding patient recruitment, an investigation of patient attitudes throughout Europe is needed. The platform should also handle patient information and education using a pan-European format (multi-lingual) in public relations, websites, brochures. etc.

(ii) A trial computer toolbox for clinical researchers as a joint venture project between drug companies

This concerns IT companies, hospitals, clinical researchers and contract research organisations (CROs). The toolbox should be based on open systems technology and be web-based, making it accessible to all researchers. The output should be compatible with Good Clinical Practice (GCP) and have a multiple platform format that allows optimal interchange. It should be secure and privacy protected.

(iii) Biomarker research should be prioritised
Good proposals are needed to promote technologies for specific chronic disease areas. Research plans should be clearly defined and supported by the European Medicines Evaluation Agency (EMEA), a clinical research group and at least two drug companies. Validation of the target, using genomic programmes to follow certain mechanisms, is important as this relationship is usually unknown. The markers could be extended to subtype responders/non-responders (improved efficacy/safety ratio/predictive adverse effect risk). For example, a typical project of great health importance is the risk of thrombosis after oral contraceptive – a project that can and will not be readily tackled by industry. Projects may include biochemical, genetic, imaging or challenge studies or disease models. Translational aspects may also be included on how to modify existing technology for use in trials.

7.1.4 Networks, interplays and platforms for future drug development

Potential projects include:
(i) Identify "hot spots" of drug development failures
These hot spots concern safety, toxicology, pharmacokinetics (ADME) and pharmacodynamics, drug delivery and clinical trials. They could be prevented through defined platform research programmes established through networks that involve academia, industry and regulatory authorities.

(ii) Define process tracks, which address the major need to improve and accelerate successful drug development
These tracks concern pharmacogenetics, bioinformatics, epidemiology, simulation and modelling and data management.

(iii) Establishment of a body to integrate the data obtained from the different tracks
The data created/collected could be published through a manual of best drug development practices: Good Drug Practices (GDP).

(iv) Create technological platforms
Platform working groups should be appointed to establish technological platforms with the aid of public funding. These platforms could concern safety, pharmacokinetics, drug delivery and clinical trials and include an action plan involving academia, industry and regulatory authorities.

(v) Implement process tracks
These involve pharmacogenetics, bioinformatics, simulation and modelling and data management.

(vi) Further, "hot spot" platforms to be addressed.
Projects to be defined by the platform working groups include, for example, the generation of data banks, repositories, pilot plans for biologicals and the immunogenicity of biologicals.

(vii) Establishment of training and educational activities
Identified needs to be addressed. A common syllabus for continuous education in Europe would be very valuable.