New Safe Medicines Faster:

How to rethink and accelerate the development and approval of innovative, new medicines for faster patient relief

Report from a workshop held from April 28-29, 2003, at the Scandic Hotel, Copenhagen, Denmark.

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Executive summary
Modern scientific knowledge and technology present a realm of opportunities for the European pharmaceutical industry to cultivate new, safe and effective medicines. Sadly, many of these opportunities are going to waste. Outdated development and approval procedures and weak ties between key players within industry, academia and regulatory authorities today pose a major barrier to pharmaceutical progress – to the detriment of patients suffering from illness and disease and the competitive ability of European industry.

To reverse this situation, new technological platforms and organisational initiatives are needed for a concerted pan-European effort involving all stakeholders in the highly complex drug development process. Equally important is integration and collaboration between the EU’s 6th RTD framework programme (FP6), EUREKA and other public bodies that fund projects aimed at modernising and promoting European drug development. Such joint funding, particularly by FP6 and EUREKA, is vital to ensure a pan-European drive with maximum impact.

The European Federation of Pharmaceutical Sciences, which has worked with the “New Safe Medicines Faster,” (NSMF) initiative for three years, and the Danish chair of EUREKA were behind a workshop aimed at determining a strategy for making new, safe medicines more rapidly available to patients, aided by recent scientific advances.

The workshop, held from 28-29 April 2003, identified the strategic research projects and organisational initiatives most urgently required to bring about faster drug development and approval. At the same time, it clarified the possibilities for future combined financing by FP6 and the EUREKA.

More than 60 representatives from the pharmaceutical industry, academic institutions and regulatory authorities participated in the workshop. The result was a series of recommendations:

- A holistic approach to drug development and research is necessary to pull together relevant disciplines and specialists from industry and academia and promote earlier, more proactive involvement by regulatory authorities to alleviate the existing, lengthy approval procedures.
- Two Technological platforms are required – one for non-clinical (exploratory) and one for clinical development. This would provide small and medium sized high-tech pharmaceutical and biotech companies, which have yet for experience the complete lifecycle of a medicine, the possibility to interact in a much needed knowledge-sharing environment. These platforms of expertise should be established to provide scientists with multi-disciplinary modern technology and give the new biotech companies, with their advanced discovery skills and methodology, a greater insight into downstream drug development.
- New predictive methods, in the form of modelling and simulation, are important to enable efficient decision-making and establish proof of concept at an early stage during clinical trials.
- New technologies for better drug selection, delivery and targeting should be developed as a priority. Besides, there is a need for new, optimised pharmaceutical materials, technologies and processes.
In the clinical phase of drug development, better patient information systems, a computer toolbox for trials and new validated biomarkers for chronic disease are required. This is particularly important as the field of individualised drug therapy opens up.

Activating and gathering the right European players for innovative drug development projects depends on efficient leadership – creating a powerhouse which, through strategic planning, is capable of coordinating and organising research and development topics of interest to industry.

To get the ball rolling, public funds to the tune of some €75,000 are needed immediately to finance a secretariat and follow-up events that will pursue the workshop’s recommendations. Additional grants from FP6 are also required but, as this money will not be available until next year, the impetus created by the workshop may by then have diminished, making it more difficult to organise the various interested parties.

The outline for a plan to promote the NSMF initiative up to 2008 is given below.

Funding programmes in support of drug-related research exist within EUREKA and FP6, the latter covering integrated projects, networks of excellence and technological platforms that are large enough to accommodate EUREKA consortia, clusters and umbrellas. Such FP6 funds are allocated on the basis of a competition, calling for proper organisation of all involved and detailed preparation of the applications. To
pursue this, initial funds are necessary. EUREKA initiatives could be established in parallel, focusing on some of the more developed projects identified in the New Safe Medicines Faster package.

As the workshop concluded, joint EUREKA and FP6 funding of an initiative involving industry, academia and regulatory authorities is the most appropriate means of setting a new European standard – bringing new medicines onto the market faster and more cost-effectively and, at the same time, breathing new life into Europe’s pharmaceutical industry.
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1 Preface
The future of European science and technology and the competitiveness of European industry are highly dependent on the European Union’s Research, Technology and Development Framework Programme (RTD FP) and funding from EUREKA. Particularly projects that receive joint funding from these bodies are likely to have a significant impact on the selected research topics.

In recent years, the European Federation for Pharmaceutical Sciences (EUFEPS) has worked hard to promote drug development within Europe’s pharmaceutical sector, mainly through the New Safe Medicines Faster (NSMF) initiative. Pharmaceutical progress is currently restricted by the fact that academic research is often fragmented and does not meet all the needs of industry. Implementation of new methodologies, processes and techniques is also hampered by insufficient research, lack of skilled personnel, stiff rules and too little interaction between the active players.

The first NSMF workshop was held by EUFEPS in March 2000 in Brussels. The second workshop was organised in recognition of the rapid technological developments that have taken place since then and the need to identify current barriers to drug development and research. Organised by representatives from EUFEPS, the Danish Medicines Agency, industry and the EUREKA Chair at the Danish Ministry of Science, Technology and Innovation, the workshop established ways to improve the speed and efficiency of drug development, outlined tangible projects and determined the organisation and funding opportunities.

This report is a compilation of the bottom-up input received from the second NSMF workshop, held from April 28-29, 2003 at the Scandic Hotel in Copenhagen. We are indebted to the lecturers, session chairs and rapporteurs, and participants for their contribution. Without them, this report could not have been produced. Our thanks also go to those who received and supplemented the written text.

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Better, faster and more effective drug development in Europe

As the secrets of the human genome are unravelled and biotechnology progresses by leaps and bounds, the European public has high expectations with regard to new medicines and therapies for serious diseases. But the general view, particularly among patients, is that the development of new medicines is too long and drawn out – a problem to which no simple answer exists.

Traditionally, the entire drug development process is stepwise and has been divided into three largely separate phases: discovery, pre-clinical and pharmaceutical development, and clinical development in order to meet regulatory requirements. Today, these phases need to be revised to form a smooth, seamless procedure, ensuring all knowledge and data are maintained and put to maximum use throughout the process.

Drug discovery and design involve research topics linked to the identification of a drug target – where a medicine should work – and preparing the target for the screening of active leads, usually a selection of compounds stored in large libraries. When selected, the drug candidate is subject to additional functional testing, chemical structure elucidation, and optimisation in terms of potency and efficacy. Exploratory development then characterises the candidate’s metabolic behaviour in organs and defines and designs a production procedure and drug formulation. Additional in silico, in vitro, in vivo and animal testing is also performed.

When the drug candidate has passed these tests to the satisfaction of the investigator and the regulatory authorities, it is ready for human tests, first in healthy volunteers and, later, in a group of patients. Multi-centre clinical trials involving large groups of patients complete this clinical development phase, which tests efficacy and safety. Finally, all the results are evaluated in terms of quality, safety and efficacy, first by the pharmaceutical company and, then, by the regulatory authorities. Only then is the medicine ready for commercial production and sale to the benefit of patients.

Devolvement within genomics, proteomics, metabonomics and modern chemistry technologies has had a major impact on the later phases of drug development, which have been forced to match the speed of discovery. Unfortunately, this appears to have lowered the quality of the drug candidates brought forward, with a high failure rate as a result. A number of commercial drugs have even been withdrawn from the market following the emergence of rare but severe side effects. As a result, the number of new, innovative drugs introduced to the global market has been halved over the last three years, despite increasing investment.

Since financial constraints limit the ability of industry to increase its development capacity, new ways to develop medicines are in great demand. The complex, multi-disciplinary and strictly regulated nature of the drug development process means this is no straightforward task. Only a holistic approach can succeed.

New scientific knowledge and technology, involving nearly all natural science disciplines, must be developed and exploited. Traditionally academic institutions concentrate on basic science, supported by public funds, while industry takes care of...
applied research and development – roles that are currently being partly redefined thereby adding to the complexity. The regulatory authorities, though, have the final say on the introduction of new technologies. If successful change is to take place, the authorities will have to drop their typically reactive, controlling stance and adopt a new, more proactive role. The status quo is no longer sufficient.

European society today includes many other stakeholders involved in drug development, including patients, healthcare personnel, ethicists, healthcare providers, governmental health authorities, each of whom speak with their own national voice rather than representing a united European forum.

The question is: who should take the lead in changing the drug development situation in Europe which must take place? Pharmaceutical companies compete and do not want to support their competitors in the field. The regulatory authorities hold back due to their role as a controlling agency. Academic institutions are supported by national subsidies, barring them from European initiatives. That leaves the European Commission. Here, funding has to follow the rules of the RTD Framework Programmes, which require relevant topics to be announced and involve a lengthy procedure. Applicants also have to organise themselves in pan-European groups – a task that requires a certain amount of resources before applying for funds can even begin.

But there is another force in Europe capable of organising and coordinating the stakeholders – a force comprising idealistic scientists who are involved in the many aspects of drug development and are already linked through non-profit-making European networks. As they declared at the workshop, they are ready to take on the organisational task so public funds can be released and the shift towards new safe medicines faster can begin. Joint funding by EUREKA and FP6 would be a major step forward in this direction.

There is no doubt that such an initiative would strengthen and secure the competitive power of the European pharmaceutical industry. But time is short. The USA has already begun considering the shortfall in new, approved medicines, and the Food and Drug Administration (FDA) has appointed a new director specifically to overhaul the existing regulatory procedures and facilitate the approval of new medicines. If Europe is to secure a global lead, action must be taken now.

2.1 Patient perspective

Over the years, the pharmaceutical industry has delivered a series of new and improved medicines, albeit at continuously increasing costs. These costs are now so high that they prohibit certain patients groups from gaining access to the best available therapies. This trend combined with the decline in productivity is a cause for concern, as it can only lead to one thing – even higher prices and more restricted use of the few new drugs launched on the market.

Patient organisations are putting pressure on politicians. A good example is the impact the AIDS community has had on generating new AIDS medicines, for which a new, accelerated development and approval process has been accepted and is now pursued. However, when it comes to improving the drug development process in general, the
present organisational structure is no longer appropriate. For this reason, patient organisations have heavily supported FP6 initiatives for an integrated research approach, in which they are actively involved. Similarly, the recently adopted EU orphan drug is a step in the right direction for diseases that affect a relatively small number of patients.

Such a proactive attitude by the authorities is crucial in the effort to secure new innovative medicines in European patients

Current methods for informing patients about safety can be improved using the package insert approach. Internet-based patient education and support and patient involvement in methods to record adverse events would also from part of a reengineered drug development process. Specific diagnostic tools are needed in the case of chronic diseases to ensure physicians prescribe the right medicine at the right dose from the outset. At present, the application of such treatments is often not optimal.

2.2 Ethical perspective

National legislation, a platform for European unity and ways to define common ground between members of the European community are the three challenges that face the ethical perspective of drug development in Europe.

Today national regulations tend to enshrine a set of norms and values maintained by national ethical committees and boards. If ethics are also seen as an expression of national politics, they may be regarded an instrument of political agendas – and significantly hamper efforts to achieve European unity.

Due to the lack of a common ethical platform between member states, it is not really clear whether it makes sense to seek unification at all as any cooperation or act of harmonisation assumes a common level of understanding on a particular issue. Where no common ground exists, international legal instruments are mere expressions of power rather than common insight into fundamental values.

Ways to define some common ground are equally hard to find. Within Europe, it appears to be increasingly difficult to formulate principles that reflect underlying values, such as integrity, freedom and goodness. Some suggest, instead, that agreements should be made on what to reject, such as atrocities, divided societies, medical paternalism and secretiveness.

Within the pharmaceutical industry, these main problems could be dealt with in the following way. The needs of society and the stakeholders involved should be clearly defined and ethics more fully integrated into R&D – the FP6 already demonstrating the feasibility of the latter. Furthermore, international R&D standards need to be defined, just as has been done in the Nuremberg Code, the Helsinki Declaration and Council of Europe treaties. The establishment of international supervising mechanisms would ensure these standards are applied. Easy access at European level and beyond to adequate information about ethical aspects (traditions, arguments, evaluations) would give these standards added strength.
A willingness to reduce national influence for the sake of greater European benefit is the most important precondition of a common ethical platform. To a certain extent, this has already been present in drug approval, but it needs to be extended to the clinical development phase. Pan-European trials would then be greatly facilitated, particularly for orphan diseases that affect few patients in each region.

### 2.3 Regulatory perspective

The primary objective of the regulatory authorities is to protect patients by ensuring the medicines on the market are safe and effective. At the same time, the approval process should not incur extra costs for the pharmaceutical company by delaying the launch of new medicines or imposing unnecessary requirements for drug development.

Regulatory requirements need to evolve to reflect scientific progress. In preclinical development, new approaches are required with an enhanced ability to predict drug safety and reduce the use of animal tests. Comparative studies should also be encouraged. Toxicogenomics, transgenic animal models and mathematical modelling/simulation are among the areas for improvement. Clinical development, on the other hand, needs new insights into pharmacogenomics, the genetic basis of disease and effect of environmental factors. Such initiatives will lead to faster innovation and give the authorities an improved insight.

Before regulatory requirements can be altered, disease characterisation has to be improved. This involves improved knowledge about the genetic basis for disease, environmental effects, pathogenesis and pathophysiology. The aim is to ensure that the spontaneous progression of disease is more uniform and that patients react to drugs in a similar way without side effects caused by their individual genetic makeup.

With regard to pharmacogenomics, it has with the right methodology the potential to identify before a clinical trial responders from non-responders. Therapeutic confirmatory trials in responders will then promote a uniform response to the drug and further decrease response variations in individual subjects. This may lead to a reduction in the size of the trials needed to confirm safety and efficacy. Whether or not pharmacogenomics can reduce adverse side effects through individualised therapy is, though, currently uncertain. Is the level of knowledge sufficient to rule out any adverse event? And what about the influence of the environment on the individual’s predisposition for the disease? More research of these aspects is required.

The main issue from a regulatory point of view is that the predictability of tests should always be evaluated in terms of efficacy and safety, as stakeholders may have differing motives for reaching a common goal. Increased interaction between regulatory authorities, academia and industry from the initial planning phase through to the market launch of a new drug would undoubtedly benefit all parties. But before new techniques and methods can be introduced, there will be a learning phase in which the regulatory authorities must participate. This could be facilitated by a research arm connected to the authorities, stimulating the introduction of new techniques and methods designed to make drug development smoother and faster. Regulatory agencies in the US have already established the usefulness of this approach by encouraging the evaluation of new technology.
Cooperation of this kind would give European regulatory bodies a more proactive role. Thus, a commitment, with adequate resourcing, to undertake research by European regulatory authorities, who have access to an enormous body of data across many compounds and disease state, is highly desirable, if not essential. The authorities would then become involved in joint research projects with industry and academia setting future requirements for pre-clinical, toxicological and clinical tests and the production of complex biopharmaceuticals. Similarly, new ways of conducting clinical trials also call for cooperation among the various stakeholders. These include procedures for adaptive trials, learn and confirm trials and limited drug approval with stricter post-marketing monitoring and follow up.

The need for improved post-registration safety and pharmaco-vigilance methods is highlighted by several studies carried out in the US. Patients who developed adverse symptoms were in hospital for 1-4 days longer than patients who did not, incurring additional hospital costs of up to $5000 per patient. Removal of this health care burden is an important goal in developing new, safer and more effective medicines.

2.4 Industrial perspective
Traditionally, the pharmaceutical industry has relied on a few high-selling products, so-called blockbusters, which provide the world’s leading pharmaceutical companies with almost half their total revenue. Today, with blockbusters on the decline, the industry has become forced to adopt a portfolio approach, selling a wider number of drugs for smaller markets.

Annual R&D expenditure has increased over the past decade by a steady 10% a year. But the number of novel medicines based on new compounds has fallen, only half as many entering the market in 2002 compared to 1997. With the cost of bringing a drug onto the market now around €800 million, the pharmaceutical industry is facing the major challenge of developing new products without relying on blockbusters to pay for less successful medicines. There is also less money to pay for drug candidates that fail at a late stage of the drug development process.

Over the past 10 to 15 years, large investments in new technology to optimise the discovery, exploratory and clinical development phases have not improved the process of drug development, which still takes anything from eight to 11 years. This suggests that the traditional drug development process has no longer got the potential for further major improvements. Instead, it requires a major overhaul and reorganisation and much closer collaboration between academia, industry and regulatory bodies.

Recent advances within genome research, pharmacogenetics, metabonomics, in silico modelling and other new techniques point the way towards individualised medication based on far more specific diagnostic systems than those used today. This requires a better understanding of disease processes by reverse discovery, with clinical pathophysiology driving the drug discovery process rather than, as now, high throughput screening where invalidated targets are tested for proof of concept in the clinic. Although the genomic revolution has generated more leads, the methodology currently available for selecting the most promising candidates is inadequate, which means valuable leads may be lost. A new concept for the entire research, development and approval process is, thus, essential to keep expenditure down.
Within contract research organisations (CROs), the current focus is on process improvements such as electronic data capture, improved patient recruitment and data management and electronic regulatory submissions. However, as the research conducted by the CROs is very limited, there is a risk that they may work on improving clinical trials that are of little or no value.

The many new small and medium-sized enterprises (SMEs) working with the development of new drug candidates are hard pressed due to a lack of experienced drug developers and the increasing complexity of the development process – a problem that could be solved by a commitment to more practical experience in the science of drug development and the establishment of European technological platforms.

### 2.5 Clinical perspective

Pharmaceutical companies tend not to be very innovative when it comes to clinical development. Once a drug candidate becomes ready for clinical trials, the company wants to get through them as fast as possible according to established procedures. To date, the time saved during this phase has mainly been due to better organisation and rationalisation than true innovation – a trend recently reversed by incidences of commercial drugs being withdrawn due to rare but severe side effects.

The key to success in the pharmaceutical industry is the ability to understand the biology behind disease rather than the chemistry – in other words, reverse discovery. For this reason, collaboration in mechanistic research must bring industry and academia together. Academic clinical centres should be strengthened and put back in the driver’s seat to identify and help establish new ways of testing medicines’ efficacy and safety. Courses are required to provide clinical investigators with investigation certificates. To be successful, this work has to be conducted in tandem with forward-thinking regulatory authorities.

There are many new options to consider, including question-based development, learn and confirm trials, adaptive clinical trials, and better characterisation of patients for drug development. In addition to research into and validation of drug targets, biomarker development is of outmost importance.

### 2.6 Academic perspective

Academic institutions in general are engaged in all phases of drug development. Scientists from schools of pharmacy and other related faculties throughout Europe conduct unique research, in some areas of emerging importance representing world-leading groups. Most of these schools and faculties, though, are of limited size and only cover part of the drug development process. Coordination and integration across research institutes, universities, countries and continents would ensure optimum gain from these activities. As time goes on, academic research is becoming increasingly reliant on time-limited project funding by the public or private sector – implying decision-making at all levels. The support currently obtainable from FP6 represents a major step ahead, but it is not sufficient.

Some efforts are being made to draw pioneering academic research groups together, for example, by the European Clinical Research Network (ECRIN). But a broader
A technological platform is still lacking. Inspired by the NSMF initiative, a new national programme has been proposed in the Netherlands: The National Technology Platform for Re-engineering Drug Discovery. The programme focuses on both the molecular basis of disease mechanisms and disease monitoring, and the selection of clinical drug candidates. This is expected to lead to new national facilities in the form of advanced animal models, accelerated lead selection and drug profiling in human tissues.

More European programmes of this type would be of considerable value. In cooperation with supranational initiatives, such as FP6 and EUREKA, the synergy and impact they create could be significantly increased.

2.7 Public funding perspective

The EU 6th Framework Programme, adopted in December 2002, introduced the possibility for European public funding of research projects linked to drug development. At the same time, it established a series of research priorities under the heading Advanced Genomics and its Applications.

For rational and accelerated development of new, safer and more effective drugs, FP6 cites “pharmacogenomic approaches; development of new diagnostics; development of new in vitro tests to replace animal experimentation; development and testing of new preventive and therapeutic tools, such as somatic gene and cell therapies (in particular stem cell therapies, for example those on neurological and neuromuscular disorders) and immunotherapies; innovative research in post-genomics, which has high potential for application...”

The programme also highlights the need for technological platforms for developments in new diagnostic, prevention and therapeutic tools. “In the context of preventing and treating diseases, the objectives are to foster academic and industrial collaboration through technological platforms where multidisciplinary approaches using cutting edge technologies arising from genomic research may contribute to health care progress and cost reduction through more precise diagnosis, individualized treatment and more efficient development pathways for new drugs and therapies (such as the selection of new drugs candidates), and other novel products of the new technologies...”

The research priorities outlined in FP6 are in perfect accord with the New Safe Medicines Faster initiative. This means it is now up to the involved parties to get organised and apply for the money.

The available funds, though, are limited. The €1100 million set a side for advanced genomics has to be divided between the two FP6 areas “Fundamental knowledge and basic tools for functional genomics in all organisms.., and “Application of knowledge and technologies in the field of genomics and biotechnology for health... As drug development only constitutes part of the programmes, this leaves only some €300 million for the drug area.

EUREKA is a promising source of additional necessary funds. Among its objectives, EUREKA aims to strengthen the basis for lasting prosperity and employment in Europe by promoting the productivity and competitiveness of European industry and national economies through closer co-operation between enterprises and research...
institutes working with advanced technologies. EUREKA focuses on three basic aspects: partner search, public funding, and a bottom-up approach starting with industry. Regarding the latter, the participants determine their objectives and activities, who they choose to work with and such aspects as project cost, duration, management and how risks, results and intellectual property rights will be shared.

Since many smaller high-tech, biotech and pharmaceutical companies are involved in the drug development process, there is a strong case for combined funding of joint projects by FP6 and EUREKA. The large integrated projects outlined in FP6 already make room for clusters of more product-oriented development while the emphasis on technological platforms represents an obvious starting point for joint projects.

Combined EU and EUREKA funding would undoubtedly stimulate the necessary interaction between academia, industry and regulatory authorities. This would give industry better access to new, accepted development techniques, fuel academic research and encourage authorities to play a more active role throughout the drug development processes.

Under the auspices of FP6, the regulatory authorities would gain a neutral platform on which to interact with industry and academia in an effort to speed up drug development procedures and approval. Those involved in research and development could then focus their efforts, safe in the knowledge that all the new methodologies and techniques they employ fulfil safety requirements.

While FP6 provides the outline for research priorities, it does not specify the exact topics eligible for each funding round. Drug development technology is evolving extremely fast, and much has happened since the publication of the first New Safe Medicines Faster report three years ago. For this reason, a fresh look at NSMF priorities is required prior to the third FP6 round in October 2003.

The workshop considered only the role of the EU Framework Programme and EUREKA.
3 Organisation of the workshop

All participants attended the workshop by invitation, ensuring broad representation by the main stakeholders – industry, academia and regulators from many European countries. A total of 63 delegates attended, comprising 24 representatives from 21 pharmaceutical companies and contract research organisations, 20 academics from 18 universities, including schools of pharmacy, and 2 regulators from European agencies (see 7.2 appendix 2). Two participants represented the financial sector. Civil servants from the European Commission, EUREKA, and government ministries of Denmark and Netherlands were also in attendance. Women accounted for 22% of those present.

For practical reasons, the workshop consisted of four discussion sessions. The drug development process itself was discussed in three sessions, a fourth session looking into the organisational picture and paths for developing the New Safe Medicines Faster concept further.

The sessions had the following titles:

1. New technology (needs and options) for drug development.
3. Challenges and issues in shortening the time for clinical development, including better characterisation of patients for drug development.

Distinguished lecturers were invited to chair the sessions (see 7.3 appendix 3), for which a further two rapporteurs were nominated. The participants were asked to engage in active discussions concerning the main aspects of faster drug development under the heading of their session: rethinking drug development; concrete research projects; topics for joint projects for FP6 and EUREKA; topics for specific funding under FP6. The outcome of the discussion sessions was the subject of a report session, which was followed by a general discussion in plenum. At the end of the workshop, the organisers summarised the outcome by providing conclusions and recommendations.
4 Workshop discussion sessions
This chapter provides a summary of the four discussion sessions. More detailed information about the concrete projects can be found in 7.1 appendix 1.

4.1 Overall project proposals
Based on the detailed discussions of the sessions, the following major topics were identified as suitable for joint projects and/or individual projects funded by FP6 and EUREKA.

New technologies and tools for
- Drug selection, toxicity screening and genetic approaches, e.g. ‘drugability’ algorithms, in vitro screening systems, active transporter systems, robotics, biomarker selection, animal to man scaling, N-in-one cassette approaches, micro-dosing
- Drug delivery and targeting technologies, e.g. carriers and transporters (self-assembling bodies, such as liposomes, micelles and nanoparticles), bioenhancers and homing devices
- Advanced pharmaceutical materials, technologies and processes

Prediction methodology in the form of modelling and simulation has developed fast since the first NSMF workshop was held in 2000. These methods will become more important in the years to come but still require regulatory approval. Prediction methodology covers:

- Overall modelling of the drug development process
- Virtual pharmacokinetic models and pharmacodynamic modelling
- Biosimulation e.g. the virtual cell and patient populations; disease modelling, also in relation to pharmacogenomics
- Molecular modelling in relation to pharmacogenomics
- The creation of data libraries including population variables such as genetics, age, gender and disease

Requirements for the clinical phase:
- The development of integrated patient information systems and a trial computer toolbox
- New biomarkers for the chronic disease areas

The optimisation of individual drug therapy concerns pharmacogenomic research, including new diagnostic tools, array technology and sensor technology. Linked to this are tools for measuring safety risks and determining personal dosing and scheduling.

These projects should work together with other planned FP6-supported projects related to accelerating the development of safe medicines, for example networks of excellence for individualised medicines, pharmacogenomics, and modelling and simulation.
4.2 New technologies for drug development
This discussion session focused on the innovation and development of new technologies aimed at accelerating drug development.

4.2.1 Rethinking drug development
The dynamics of the drug development process depend heavily on scientific insights and technologies which are available within the pharmaceutical sciences and in other fields of expertise, such as IT, genomics and genetics. If properly established, this ‘technology push’ would clearly allow the pharmaceutical scientist to make fast progress in streamlining and shortening the development process for modern drugs. On the other hand, new, basic scientific questions are being raised and unmet technological needs defined: the ‘technology pull’ side.

Novel, non-existing technologies are in high demand, as a number of new promising paradigms still cannot achieve their potential due to missing links in scientific understanding and technology. Prime examples are the present gene therapy approaches. Here the lack of efficient, non-immunogenic, DNA-transport systems is a major stumbling block for the successful further development of this fascinating therapeutic strategy.

Four major technological fields were identified as priorities:

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

4.2.2 Deliverables
A full account of the deliverables discussed can be found in 7.1 appendix 1. The deliverables defined on the basis of the group discussion can be summarised as follows:

- The creation of a European platform to coordinate the development of much needed, new technologies for drug development in the non-clinical stage
- Closer interactions between the regulatory authorities and the other stakeholders. This includes a forum for discussing the value of and need for new technologies and approaches at an early stage of their development.
- Pan-European initiatives regarding: ‘drugability’ assessment, early toxicity assessment, bioavailability enhancement, biomarker selection, animal to man scaling, development of new analytical and pharmaceutical technological techniques, development of (targeted) drug delivery approaches, development of new diagnostic tests and (bio)sensors for patient phenotyping and individualised dosing.

4.2.3 Stakeholders
The following stakeholders can be identified:

- Academic partners: to develop concepts regarding the unmet needs identified by industry, regulatory bodies and academia
• Industry: big pharmaceutical companies to identify bottlenecks in the drug development process and participate in the networks
• Industry: small and medium-sized pharmaceutical and biotech companies can benefit from the creation of a research network covering all aspects of the non-clinical development phase and can also provide specific and highly valuable input based on their ‘niche’ expertise
• Regulatory bodies: to identify sections of the non-clinical drug development process where ‘regulatory’ bottlenecks are encountered. Regulatory bodies can help to analyse the problems by providing input, participate in the discussions and, hopefully, take part in concept development in close cooperation with the other stakeholders

4.3 Modelling and simulation in drug development

The second discussion session focused on one of the most promising technological advancements in relation to accelerated drug development: modelling and simulation.

*In silico* modelling and simulation can be applied at every stage of the drug development process, from the virtual modelling of cellular function, e.g. the whole network of molecular interactions involved in cell biology, to modelling virtual populations. These methods are considered the most likely source of the power and tools required for the much-needed reorganisation of drug development, providing the following:
• A framework for the continuous integration of drug development knowledge through a European web-based network
• Improved study designs and more informative studies
• Easier answers to regulatory questions, possibly eliminating the need for more clinical studies and ensuring an improved benefit to cost ratio

For this to happen, it will be necessary to:
• Encourage the development and application of modelling and simulation
• Enhance the confidence of various partners in using models and their outcome
• Create models that are as mechanistically-based as possible

The following partners are equally important in achieving this goal:
• Academic partners: to develop the theoretical and conceptual basis for the model and perform quality assessment and control of components
• Big pharmaceutical companies: to conduct retrospective and prospective analyses of the application
• SMEs: to provide specific information (IT, genomic etc)
• Regulators: to conduct retrospective analyses of the application and establish good practice, i.e. by providing anonymous data for the validation of models by academia and industry and promoting confidence in modelling.

Further dedicated funding, integrated projects or networks of excellence under FP6 regarding modelling and simulation would greatly improve this process.
4.4 Challenges and issues in shortening the time of clinical development, including better characterisation of patients for drug development

Chronic, non-communicable diseases carry the highest burden for the European community. Diseases such as cancer, cardio-vascular and rheumatic diseases, diabetes, neuro-psychiatric disorders and so on\(^1\) should be subject to a concerted European initiative covering one or more of these areas. The most rewarding disease areas with the greatest medical need and the greatest chance of success should be identified for public support:

(i) Knowledge generation is the basis for effective development

- Greater knowledge about disease mechanisms and better understanding of disease/patient heterogeneity are necessary. Drug design should be based on in-depth knowledge of the underlying biology of the disease to ensure treatment of the disease itself and not only the symptoms.
- The generation of clinically relevant, validated biomarkers is in great demand. The identification of responders versus non-responders will greatly advance the treatment of patients both in terms of efficacy and safety. The European Medicines Evaluation Agency (EMEA), a clinical research group and at least two drug companies should support the research plan

(ii) Improvement of the process

- Establishment of European IT and process standards for clinical trials based on the EU GCP directive on clinical trials\(^2\).

(iii) Patient recruitment and data management

Patient recruitment is often the time limiting factor for clinical trials

- A pan-European information campaign should inform the public about the safety of trials and the importance of participating for the benefit of health care.
- An EU website, where patients can be matched to trials, would make it easier to find appropriate patients for trials and facilitate cross-regional collaboration. An integrated European database should be created with built-in security and confidentiality
- A pan-European IT infrastructure for clinical trial data management is technically within reach. If standards are established and adopted, this could eventually lead to large reductions in overhead costs for industry and wider possibilities for academics to study healthcare intervention in a pan-European collaboration. This would improve the competitive position of Europe versus the US and Japan considerably

A trial computer toolbox for clinical researchers would guarantee the rapid availability of safety and efficacy data both during and after more effective post-marketing surveillance.

\(^1\) [http://www.who.int/hpr/archive/expo/futures06.html](http://www.who.int/hpr/archive/expo/futures06.html)

4.5 Networks, interplays and platforms for future drug development

The fourth discussion session dealt with organisational initiatives aimed at advancing and promoting the New Safe Medicines Faster concept, covering concrete topics and projects initiated through dedicated funding by FP6 and strategies for establishing joint FP6 and EUREKA projects. Another important question was how to pave the way for a complete rethinking of the drug development and approval process.

In order for the European pharmaceutical industry to gain momentum, a dedicated programme must be implemented to meet its particular drug development needs. This could be achieved with start-up support from EUREKA and the more long-term financial backing of FP6, drawing on EUREPS networks of expertise and political, academic, regulatory, industrial and patient organisation input. In this connection, the widespread and loosely organised pharmaceutical faculties represent an untapped resource.

The current drug development programmes run by European industry require considerable improvement in their later stages. Among the reasons for the high failure rate are:

- Insufficient predictability of the animal models used
- A lack of defined and validated strategies enabling early prediction of a drug’s effect prior to human trials
- A lack of systematic (retrospective) analysis of the correlation between effects on animals and effects on humans
- Insufficient validated biomarkers
- A lack of databases held by regulatory authorities to register failures
- Insufficient emphasis on understanding the biology of chronic diseases.

If these barriers are overcome, it will become possible to allocate resources to the development of successful and beneficial medicines with an improved cost benefit ratio. This is likely to lead to reduced use of animals, increased patient protection and safer drugs.

The complex development process relies heavily on modern technology. Every time innovative inventions and methodologies appear, new routes open up for the faster and more efficient generation of medicines. But this new technology has to be integrated in the entire development process. To this end, publicly supported technological platforms could provide an arena where the necessary research and validation could take place. These platforms may coincide with FP technological platforms or stand alone, dealing with, for example, pharmacokinetics and pharmacodynamics, ADME, safety, drug delivery and clinical trials. The platforms should also include valuable input from regulatory authorities, patient networks and large pharmaceutical companies. In the figure below, the development process is illustrated as a matrix with horizontal tracks following the time line of drug development, passing along the way the vertically placed platforms that denote the various disciplines for drug development.
If organised on a large scale within the European Research Area, such platforms would be of tremendous value to the European pharmaceutical industry, especially the small and medium-sized biotech companies which are often not well-prepared for the further development of identified drug candidates. According to co-organiser of the workshop, Fritz Bühler, out of 680 recent business proposals, only five have a professional development plan.
5 Proposed programme and deliverables

5.1 Research matters
One of the workshop’s objectives was to revise the research topics that take first priority in the push towards rational and accelerated development of new, safe and more effective drugs. In the three years since the first NSMF workshop, the drug development process has evolved considerably, creating the need for a fresh look at the situation; the raison d’etre of this workshop.

The results of this appraisal closely match the EU’s FP6. For this reason, the prioritised research topics should be taken into consideration in the coming allocation of FP6 funds under theme 1.

In the same way, the topics described in the NSMF concept are suitable targets for EUREKA funded projects. A parallel effort with FP6 research support would significantly enhance the impact of such research on the pharmaceutical industry.

5.1.1 Research topics
The research topics have been identified and listed in Chapters 4 and 7.1 appendix 1 where they are described under the headings: clinical aspects, prediction methodologies in the form of modelling and simulation, and new technologies and tools. Functional gene analysis, the development of disease models and non-invasive measuring, information technology, process optimisation and personalised medicine optimisation are other important aspects.

5.1.2 Technological platforms for drug development
The technologically complex and heavily regulated nature of the drug development process calls for a corresponding strong organisation of all the stakeholders involved. Within FP6, the concept of technological platforms has been established for this purpose but remains to be exploited (cf. section 2.7). Here, we propose the establishment of FP6-funded European technological platforms to promote, assist and renew drug development.

Two technological platforms would be appropriate: one for non-clinical (exploratory) development and one for clinical development. A third focusing on chemistry, manufacturing and control may also be considered. The platforms could also be linked to topics such as safety, drug delivery or similar. The overall aim is to gather a multidisciplinary team to work basically with generic research and apply the knowledge acquired to real projects.

Despite the superb creativity of European scientists, the fragmentation and diversity of European member states have made it hard for the stakeholders to discover, develop and deliver new drugs. The existing development and approval systems simply cannot match the speed of innovation. Differences in national regulations, including ethical aspects contribute further to these difficult conditions. One of the major barriers is the poor interaction between the major stakeholders - for example, contact with the regulatory authorities lacks openness and transparency. Had European stakeholders been better organised, it is our belief that the past decade’s job drain from Europe to the US could have been prevented.
The increasing emergence of biotech companies in Europe is very encouraging. However, most of the SMEs involved in drug discovery has little and no experience in downstream development. This fact seriously hampers the future expansion and business success of these companies. Coordination of the pool of know-how would substantially reduce, if not avoid, duplication of the effort.

A European technological platform established to gather and research the necessary pre-competitive technologies would be of immense value to the SMEs, elevating them to real drug developers. Furthermore, the platform could provide neutral territory where regulators, industry representatives and academic scientists could meet and prepare for a rational reorganisation of drug development and approval. Here, research on topics and processes identified as barriers to a more streamlined and rational drug development process could be conducted. The platform could also serve as a forum for patient organisations and healthcare providers to voice needs such as first priority medicines for European citizens.

Foresight, leadership and drive are required to make such a platform successful. We believe the time is ripe and that the current grim situation will encourage the necessary cooperation between large and small players in the pharmaceutical industry (see 7.4 appendix 4).

The allocation of dedicated FP6 funds and exploitation of the new tool technological platforms are needed to spur the stakeholders into action. The enthusiasm and potential benefits expressed at the workshop show that the necessary interest and leadership capability are there.

5.2 Organisational matters
A list of bottlenecks, barriers and research requirements for the current drug development process is of little value if it is not accompanied by a plan for promoting and implementing the projects and activities listed. The plan should be carried out on the basis of shared cost risk using public money raised through FP6 and EUREKA and, in the long run, involving the European Research Area (ERA) concept. It should be noted that Finland, Austria and the Netherlands already operate drug development programmes.

5.2.1 Project organisation for promoting the NSMF concept
The plan for stepwise implementation and promotion of the NSMF initiative was arrived at during the discussions in session 4 and in plenum. The concrete plan comprises 5 consecutive steps, each providing the precondition for the next.

The time-line for financing the NSMF initiative:
Step 1: Defining needs and future funding possibilities.
This step was carried out by the workshop. From here, recommendations in the form of dedicated funding for technological platforms, integrated projects (IP) and networks of excellence (NoE) under theme 1 of FP6 will be forwarded to EUREKA and the European Commission. The recommendations include outlines for projects, which could be supported by EUREKA alone or by joint projects between EUREKA and FP6, and an organisational plan.
Time horizon: Completed

Step 2: Activation of stakeholders for future projects.
The pharmaceutical industry, academic institutions, regulatory bodies, hospitals, healthcare providers and patient organisations are notified to rouse their interest. This is currently done by the workshop organising team, which calls for an expression of interest in NSMF through public-private partnerships. Step 2 will involve employing an experienced drug developer part-time to serve as executive secretary to the workshop organisation team, with responsibility for coordinating the initiative’s progress and obtaining EUREKA backing for step 3.
Estimated budget: About € 75,000 to cover salary, travel and meetings
Time horizon: July 2003 – July 2004 with the following activity schedule:
<table>
<thead>
<tr>
<th>Activity</th>
<th>Time-span</th>
<th>Deliverables</th>
<th>Responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Call for expression of interest from stakeholders</td>
<td>May 13, 2003 to August 1, 2003</td>
<td>List of interested stakeholders</td>
<td>Workshop organising committee</td>
</tr>
<tr>
<td>Establishment of secretariat to organise and coordinate activities</td>
<td>June 2003 to August 2003</td>
<td>Employment of a executive secretary for the NSMF concept</td>
<td>Workshop organising committee</td>
</tr>
<tr>
<td>Formulation of proposals for specific FP6 calls</td>
<td>May 2003 to August 2003</td>
<td>Proposals for calls</td>
<td>Workshop organising committee</td>
</tr>
<tr>
<td>Prepare for application for Specific Support Action in FP6</td>
<td>August 2003 to November 15, 2003</td>
<td>Submission of application</td>
<td>Executive secretary</td>
</tr>
<tr>
<td>Establishment of a core group to expand the projects defined in the workshop report in more detail</td>
<td>August 2003 to June 2004</td>
<td>Conclusions from concurrent fora / platform discussions on projects</td>
<td>Executive secretary</td>
</tr>
<tr>
<td>Locate industry and academia for co-financing projects under NSMF</td>
<td>August 2003 to June 2004</td>
<td>Concurrent updated list of potential partners</td>
<td>Executive secretary</td>
</tr>
<tr>
<td>Formulation of projects within EUREKA clusters</td>
<td>January 2004 to 2008</td>
<td>Detailed project plans</td>
<td>Cluster partners</td>
</tr>
</tbody>
</table>

**Step 3: Creation of steering group**
A group of dedicated stakeholders, many of them workshop participants, is established to create and organise in cooperation with the executive secretary the basis for the second round of fund-raising. This is necessary to keep the group afloat while preparing for pan-European networking within the concept of NSMF. Step 3 may be supported with money dedicated to such activities within FP6 (specific support actions (SSA) and/or ERA support) and contributions from the stakeholders. The group will also act as a think tank, analysing and rethinking the drug development and approval process.


**Step 4: Joint applications to FP6 and EUREKA and implementation**
Through meetings and workshops on the technological platform(s) created by the steering group, the stakeholders form groups, consortia and clusters dedicated to large projects that may be supported by EUREKA funding and/or are eligible for the third round of FP6 funding under the heading Technology Platforms, Integrated Projects and Networks of Excellence.
Budget: Project size may range from €5-20 million. This can be repeated for the fourth FP6 round.

**Step 5: EUREKA projects on the NSMF theme**
Through the established secretariat function, the organisation of stakeholders and the many project ideas, sole EUREKA projects are established in parallel to the jointly funded projects, adding to Europe’s competitive edge.

**Integration with national programmes to support drug development: the ERA conset.**
In Europe the following publicly funded programmes related to drug development already exist:
- Drug 2000 and 2003, FIN
- GENAU 2001, AUS
- BZIK Funding for Technology Platform for Re-engineering
- Drug Discovery, NL (under implementation)
- ECRIN. The European Clinical Research Infra Structure Network comprising Denmark, France, Germany and Italy (currently seeking FP6 funds).
- ERADRUG. An ERA research network actively involved in drug discovery and development at national and regional level (currently seeking FP6 funds).

Further activities may be initiated during the Dutch EU Presidency in the second half of 2004, as the Dutch Ministry of Research plans to support the initiative “Priority Medicines for the Citizens of Europe... This concerns therapeutic and preventive gaps, white spots on the hot pharmaco-therapeutic map, new ways of thinking about the future development of medicines and vaccines and their relevance to the initiative as a whole. A high-level conference is to take place in Den Haag on November 18th 2004. Time horizon: July 2004 and onwards.

Based on this master plan, many concerted projects related to innovation needs, research, validation, development and production may develop in parallel, involving existing projects, EUREKA and other national funding bodies. To ensure this, continued support from the EUREKA network is necessary.

Europe can only return to the driving seat of drug development if the legal framework for development, production and marketing is optimal and reflects the state of the art possibilities offered by research and development disciplines. To achieve this, it is necessary to plan the future rules for drug development and approval some 10 years in advance so the necessary research and validation can take place in good time. In this way, the rethinking of drug development and approval can go hand in hand with genuine research and development projects.

It is also important to remember the educational aspects. Scientists with the right skills and knowledge must be in place when the new rules are implemented. This calls for close contact with the universities involved in post-graduate training and education.
5.2.2 Management
The huge task of getting many different stakeholders from many European countries to work together calls for a strong, dedicated management team backed by the necessary network. The team should include stakeholders representing various interests to prevent any bias arising from their professional backgrounds and affiliations.

EUFEPS has been the vehicle that has pulled the wagon so far. However, the core group of executives and their resources have now been stretched to the limit, creating the need for greater involvement and additional funding.

Success depends on drawing existing European organisations involved in drug development into the network, including the European Federation of Pharmaceutical Industries and Associates (EFPIA), Emerging European Biotech (EEB), European Medicines Evaluation Agencies (EMEA), European Federation of Biotechnology (EFB), European Association of Clinical Pharmacology & Therapeutics (EACPT) and the European Association of Faculties of Pharmacies (EAFP). Despite numerous contacts, the NSMF initiative has not captured their attention due to the lack of dedicated follow-up resources. The interest of EUREKA has now renewed the effort to involve these organisations. At the workshop, a profile was identified for a group of senior representatives from industry, academia, regulatory agencies and financing bodies, people who have held high-ranking positions and who may either be retired or close to retirement - an ideal group to carry the project forward. However, in order for them to carry out their role, they need a minimum of secretarial assistance and money to cover travel and expenses. Without some initial public funds, it is doubtful whether the group could be gathered.

Another way of raising interest could be to gather forward-looking, key players within the stakeholder organisations and officials from the European Commission and EUREKA to discuss the reworking of the whole drug development process. If such a meeting could take place on informal, neutral territory without direct reporting, it may be possible to clarify the existing possibilities for promoting the NSMF initiative. Again resources are needed.

5.2.3 Time schedule
The workshop was financed by the Danish chair of EUREKA. This report reflects the results of this investment. To utilise the networking and momentum gained at the workshop, money must now be made available for the next step. While the FP6 offers excellent funding opportunities, its fixed time schedules place a considerable limit on fast promotion. The first application possibility is in November 2003, after which, if granted, spendable money will be available at the middle of 2004. This is too late if the current momentum is to be exploited. The task of making a proper application is also extensive and calls for professional assistance and cooperation. For this reason, financing for the interim period up to July 2004 is important.

Joint projects involving EUREKA and FP6 may be possible to a limited extent in connection with the November funding round. New funding rounds will be required, though, for the creation of, for example, technological platforms. This may not
happen until the third FP6 funding round planned for March 2004. Thus the first joint projects could start in mid-2005.

5.2.4 Budget
Initiating such a series of interlinked events requires proper organisation and management. This cannot be done without money. The plan relies on public European money, although, if national or industrial funding were available, the situation would look completely different.

The project could be based at the EUFEPS secretariat in Stockholm if sufficient financing was available to employ a part-time executive secretary and finance travelling and administration. It is naive to think that such a demanding project can be run on the basis of idealism alone. So, in the first instance, funds totalling €75,000 are sought.

The budget behind the initiative is built up in a step-wise manner. In this way the funding bodies can assess the group’s work. Then, if the group fails, the investment will only have been minimal.

5.2.5 Deliverables
The planned outcome for the first year is as follows:
   1. Initiate project networks and build consortia
   2. Coordinate bottom-up initiatives to avoid duplication
   3. Prepare the ground and locate industry and academia for applications for further EUREKA and EU grants
   4. Conduct strategic work to modernise the future development and approval process

Research activities are vital to facilitate innovative drug development in Europe - research that must be quickly translated into applied processes, services and products. However, due to the complexity of drug development, research grants and development capacity cannot stand alone. Coordination, organisation and management are also needed if the right combination of ideas, projects and industrial involvement is to fall into place. This requires leadership through a dedicated, objective team of idealistic managers working closely with European stakeholder organisations. This can only be set in motion by the provision of public funds.
6 Recommendations

No single European voice can claim to talk on behalf of the development of new safe medicine in Europe, making it very difficult to create a dedicated and rational effort to improve the process. Through the NSMF initiative, an attempt has been made to bring together the stakeholders’ individual initiatives into a coordinated action. This workshop report has outlined the goals and the means for achieving them.

The research areas most crucial to promoting a faster drug development process are listed, representing the frontline of current research. All are open for exploitation and involve basic research as well as more applied topics. The same is true of the projects listed in the NSMF workshop report from July 2000, which should also be consulted (www.eufeps.org).

These topics represent a good starting point for EUREKA projects, either alone or as joint projects under the large FP6 supported projects, networks and platforms. They are equally eligible for funding by the 3rd and 4th round of FP6. As a whole, the NSMF initiative is particularly well suited to the technological platform concept.

Since the existing official organisations have largely failed to coordinate and organise optimal interaction at all levels of the drug development process, new well-trusted players would be useful. The task force behind the NSMF initiative is comprised of a group of concerned, dedicated and enthusiastic people, who want the best for European pharmaceutical industry so it can produce innovative new medicines for patients with unfulfilled medical needs. But they cannot work in a vacuum. Cleverly applied public funds can set the process of rethinking drug development and approval in motion. Once the steering group for the initiative has been formed, further support may come from many sides, including FP6, stakeholder organisations and even national governments.

This report should be regarded as part of a continuing process. A few hours of brainstorming at a workshop cannot deliver final solutions. Not all aspects of the drug development process are covered and many of the issues touched upon require further consideration.
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.
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. 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.

(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

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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 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 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,
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 cannot 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/colllected 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.
### 7.2 Appendix 2: List of participants

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<th>Name</th>
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7.3 Appendix 3: Workshop programme

Workshop

How to Rethink and Accelerate Drug Development?

April 28-29, 2003, Scandic Hotel Copenhagen, Denmark

Address: Vester Søgade 6, DK-1601 København V
Tel: +45 33 143535 Fax: +45 33 321223 Email: copenhagen@scandic-hotels.com

Programme

Monday, April 28, 2003

(11:30 – 13:00 OPTIONAL LUNCH)

13:00 – 15:30 OPENING AND INTRODUCTIONS
Chair: Prof. Malcolm Rowland, EUFEPS Past-President
Room: Grand Ball Vest

13:00 Welcome
Prof. Malcolm Rowland, University of Manchester, UK

13:10 Is There a Future….?
Simon Hughes, IBM Business Consulting Services, London UK

13:30 The EUFEPS New Safe Medicines Faster Initiative: Past, Present and Future
Prof. Ole J. Bjerrum, Danish University of Pharmaceutical Sciences, Copenhagen DK

13:45 The Industry Perspective and the Workshop Rationale
Dr. Jørgen Dirach, Novo Nordisk A/S, Bagsværd DK

14:00 The EUREKA Partnership for Research Funding
Mr. J. Gorm Hansen, Danish Ministry of Science, Technology and Innovation, Copenhagen DK

14:15 The Academia Perspective
Prof. Daan J.A. Crommelin, University of Utrecht NL

14:30 The Clinical Perspective
Prof. Adam Cohen, Centre for Human Drug Research, Leiden NL

14:45 The Regulatory Perspective
Dr. Mark A. Ainsworth, The Danish Medicines Agency, Copenhagen DK

15:00 The Ethics Perspective
Dr. Lars Reuter, European Ethics Network and University of Aarhus DK

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15:15  **Organisation of Workshop Discussions**  
Ole J. Bjerrum & Jørgen Dirach & Malcolm Rowland

15:30 – 16.00  **COFFEE/TEA BREAK**

16:00 – 18:30  **PARALLEL WORKSHOP DISCUSSIONS**

1.  **New technology (needs and options) for drug development**  
   Chair: Daan J.A. Crommelin  
   Rapporteurs: Dionigo Franchi & Pia Vuorela  
   Room: Grand Ball Vest

2.  **Modelling and simulation in drug development**  
   Chair: Malcolm Rowland  
   Rapporteurs: Erik Mosekilde & Olavi Pelkonen  
   Room: Absalon

3.  **Better characterisation of patients for drug development**  
   Chair: Mark A. Ainsworth  
   Rapporteurs: Tommy Lewander & Menno van der Waart  
   Room: Hamlet

4.  **Networks, interplays and platforms for future drug development**  
   Chair: Fritz R. Bühler  
   Rapporteurs: Beatriz Silva Lima & Lars Abel  
   Room: Grand Ball Øst

5.  **Challenges and issues in shortening clinical drug development**  
   Chair: Adam Cohen  
   Rapporteurs: Alain Bouckenooghe & Marianne Kock  
   Room: Copenhagen Øst

19:30 –  **DINNER**

*Tuesday, April 29, 2003*

08:30 – 10:30  **PARALLEL WORKSHOP DISCUSSIONS – CONT’D**  
Room: See Monday Afternoon Listing

10:30 – 11:00  **COFFEE/TEA BREAK**

11:00 – 11:30  **European Framework Programme: Priorities and Procedures**  
Dr. Alfredo Aguilar, European Commission, Brussels BE  
Room: Grand Ball Vest

11:30 – 13:00  **REPORT AND DISCUSSION SESSION:**  
**OUTCOMES OF WORKSHOP DISCUSSIONS**  
Chairs: Malcolm Rowland; Ole J. Bjerrum; Jørgen Dirach  
Room: Grand Ball Vest
13:00 – 13:30  WRAP-UP AND CONCLUSIONS
Room: Grand Ball Vest

13:30  Closing of the Workshop
7.4 Appendix 4: Backgrounder

New Safe Medicines Faster:
A new concept for drug development

By Jørgen Dirach, MD.
Novo Nordisk A/S

Executive summary
Society needs more better and safe medicines but despite increasing cost of drug development productivity is falling in terms of new medicines being marketed. Time for drug development has remained fairly unchanged during the 1990’ies even though companies have worked hard to streamline processes. It seems that we have reached the limit for the traditional drug development process. It is proposed to rethink the involved processes taking into account the recent advances within genome research, pharmacogenetics, metabolomics, in-silico modelling and other new technologies and further to align the regulatory process to cope with this. The aim is to pave the way for future individualised medication based on far more specific diagnostic systems than those used today for the benefit of patients, doctors, society and industry.

Why New Safe Medicines Faster?
The EUFEPS initiative which resulted in the proposal for New Safe Medicines Faster in 2000 has had an impact on the formulation of the EU research strategies. The European Council decision of 30-Sep-2002 on “adopting a specific programme for research, technological development and demonstration: ‘Integrating and strengthening the European Research Area’ (2002-2006)”, (2002/834/EC) reads in the section on Research priorities under Advanced genomics and its applications for health:

"Research will focus on: rational and accelerated development of new, safer, more effective drugs including pharmacogenomics approaches; development of new diagnostics; development of new in vitro tests to replace animal experimentation; development and testing of new preventive and therapeutic tools, such as somatic gene and cell therapies (in particular stem cell therapies, for example those on neurological and neuromuscular disorders) and immunotherapies; innovative research in post-genomics, which has high potential for application."

All stakeholders involved are interested in accelerated development of new, safe, more effective drugs:
Patients and physicians: Faster access to more effective and better targeted drugs with less side effects
Society: New medicines that will result in better prevention and treatment of diseases to decrease health cost, days lost through sickness, and to improve quality of life
Regulatory agencies: Faster more reliable and less resource demanding review of applications for marketing approval
Companies: Speed to market to get a longer period of exclusivity before patent expiry and to get a positive cash flow the sooner the better

R&D output is declining despite heavy investment
Despite a steady increase in the global R&D expenditure over the past 10 years as well as projected increases, figure 1, the global output from the pharmaceutical industry in terms of new medicines based on new compounds is declining, figure 2.\(^7\)

Traditionally companies have been strongly relying on few high-selling products; blockbusters. Blockbusters alone contributed almost half of the total revenues of companies such as Pfizer, AstraZeneca, Eli Lilly and Schering-Plough. With the declining number of launches of new medicines combined with high number of drugs losing patent protection, the pharmaceutical industry is now moving towards a portfolio approach, selling a wide number of smaller drugs to maintain growth.\(^10\)

With a development time of 8 to 11 years and cost up to EURO 800 Mill medicines R&D is facing a major challenge in developing new

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\(^8\) Blockbusters: Products selling more that USD 1 billion per year
medicines without relying on blockbusters to pay for the less successful medicines and for attrition.

The current cost of drug development and the need for marketing muscles to regain the investment is a major obstacle for SME to enter into the late phases of drug development.

Time for drug development unchanged

Time to market for new medicines has not changed much over the past 10 years\textsuperscript{12}, despite vast investments in the industry for business process reengineering, outsourcing and other initiatives to optimise the drug development process. Thus the traditional drug development process has not changed much over the past 20 to 30 years, figure 3.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{timeline.png}
\caption{Timeline for drug development}
\end{figure}

Research and discovery has become more effective due to new technologies such as High Throughput Screening, Computational Chemistry, Combinatorial and automated chemistry which have enabled screening of compound libraries for potential effect at a rate per day that is far greater than the No. of compounds a pharmaceutical chemist can screen manually during a whole lifetime. But both the time to explore the properties of the compounds in terms of efficacy and safety in the pre-clinical and the clinical phase of development has remained largely unchanged.

Also the process of developing a large scale production process is time and resource consuming, especially for biotech compounds

The regulatory process has been streamlined

The regulatory bodies showed good progress in reducing approval times in the first half of the 1990ies, but since then approval time has been rather constant. Figure. 4\textsuperscript{13} shows approval times from submission to approval for the EU centralised procedure.


In conclusion, we have reached a limit for the speed of the traditional drug development process.

Therefore it is time to rethink the involved processes.

George Milne, PhD executive vice-president, Pfizer says in an essay about the next generation medicine: “Testing directly against human cells has two important benefits: There is likely to be less attrition later on in the development process thereby saving years of work and millions of dollars. There should also be a reduced incidence of side effects because of more specificity in identifying receptor subtypes”14.

Initiatives have been taken by the FDA to create a more transparent drug development process by developing special guidelines for brand-new technology, such as gene therapy, bioengineered tissue or drug-and-device combinations so companies can design the right studies from the beginning. This is to ensure a higher 1st time approval rate. Currently the FDA rejects half of all novel drug applications and 93 percent of cost-saving generic drugs on the first try15.

But this initiative is only patchwork. It is necessary to start from scratch and rethink all the processes taking into consideration the recent advances within genome research, pharmacogenetics16, metabolomics17, in-silico modelling and other new technologies together with the future individualised medication based on far more specific diagnostic systems than those used today.

The traditional way of thinking is that one person has one particular disease that needs one particular treatment. This has proven wrong for many chronic diseases. A good example is type 2 diabetes which

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14 George Milne, PhD executive vice-president, Pfizer Global Research & Development in World Pharmaceutical frontiers 2002/2003
16 The goal of pharmacogenetics is to identify "genetic fingerprints" that may predict a patient's response to pharmaceutical treatment. The use of pharmacogenetics replaces the trial-and-error strategy, which governs much of our clinical decision-making regarding treatment allocation in current medical practice, with individually tailored therapy.
17 Metabonomics is a systems approach for studying in vivo metabolic profiles, which promises to provide information on drug toxicity, disease processes and gene function at several stages in the discovery and-development process.
is not just a disease where the patient cannot utilise insulin. The disease also affects other systems such as the blood lipids and the blood pressure. Therefore individualised multipharmacological therapy is needed. Basically the person's genome and lifestyle will determine which organs are affected to which extent and which specific dose level is needed of which medicine to provide the optimal treatment.

Identification of which patients responds to which medicine before start of treatment will minimise the need for patients in clinical trials and lower the number of non-responders and thereby provide a faster proof-of-concept and answer the question: Does the new drug work? Furthermore this will also minimise the number of patients to experience unacceptable side effects. If this could reduce or eliminate the need for phase 3 trials, society at large would benefit.

Despite the enormous amount of information generated by the technological developments, translation into improved health care is only materialising slowly. A fresh and innovative reassessment of drug development and approval may create new break-through opportunities to

Develop new safe medicines faster
Minimise the cost of drug development
Provide better prevention, treatment and cure
Provide a better, more individualised treatment
Create the basis for a more efficient health care system

We suggest funding a pilot project to generate an ambitious proposal on how to generate a leap forward in drug development and approval with the aim of streamlining and shortening the development and approval time without compromising efficacy, safety and quality. The idea is illustrated in figure 5.
New technologies
- CA- Modelling
- Better diagnostics
- Genetic tests
- Molecular imaging
- Optimised tox.

New regulatory process

New Safe Medicines Faster: New Drug Development and Approval Process

Benefits for patients/phys.
- Individualised medicine
- Higher response rate
- Better safety
- Shorter lag time for new medicine

Benefits for society
- Lower cost of medicine
- Shorter lag time for Patients

Benefits for industry
- Speed in R&D
- Better basis for decisions
- R&D cost lower

Figure 5. New Safe Medicines Faster provide an umbrella for a number of projects to support provision of benefits for patients, doctors, society and industry.

Such a proposal should be based on open-minded discussions between stakeholders representing universities, hospitals, regulatory authorities, and the pharmaceutical industry including small and medium enterprises.
EUREKA
– a pan-European network for market-oriented, industrial R&D

EUREKA is a pan-European network for market-oriented, industrial R&D.

EUREKA supports the competitiveness of European companies through international collaboration, in creating links and networks of innovation. The objective is to bring high quality research and development efforts to the market and to use the multiplying effects of co-operation. The aim is to advance and improve the quality of life.

EUREKA is tackling the challenge of a swiftly changing business environment and offers a platform for short-term as well as strategic collaboration. It offers flexible and dynamic support, quality label and expertise for market-oriented R&D projects.

EUREKA also offers a frame for co-operation to small and large companies alike and operates through its network of members from Iceland to Turkey, from Portugal to Russia, while always remaining open to global co-operation. Today 33 countries and the European Union are full EUREKA Members, while many more countries, particularly in Central and Eastern Europe, have some form of associate status.

The mission of the European Federation for Pharmaceutical Sciences (EUFEPs) is to serve and advance excellence in the pharmaceutical sciences and innovative drug research in Europe, and to represent the interests of scientists engaged in drug research and development, drug regulation and drug policy-making. EUFEPs was founded in 1991, and it links scientific societies and associations in 25 European countries. In addition, there are around 500 Individual Members.

EUFEPs is the only pan-European body to represent the interests of scientists in industry, academia, government and other institutions engaged in drug research, development, regulation and policymaking through Europe. To achieve its objectives EUFEPs e.g. organises, co-organises and co-sponsors congresses, conferences, training courses, workshops and hot-topic events on specialised themes as well as take other initiatives, also in international collaboration.

The EUFEPs Congress (European Congress of Pharmaceutical Sciences) is organised every two years. Established conference series include: Optimising Drug Development, Optimising Drug Delivery and Formulation and Optimising Biotech Medicines. Sample topics of Training Courses are: High-throughput (HT) Drug Metabolism/Disposition, and Combinatorial Chemistry.

In 1999, EUFEPs established the New Safe Medicines Faster Project to deliver, to the European Commission (EC) of the European Union (EU), research topics and proposals aiming at strengthening the European competitiveness in innovation, development and use of new and better drugs. As a result of this, scientists could, from 2003 onwards, apply for research money for the drug development process, within the 6th EU Framework Programme for Research and Technological Development.

EUFEPs has also established the European Journal of Pharmaceutical Sciences and a regular Newsletter. There are three EUFEPs awards: The Giorgio Segré Prize, the Young Investigator’s Award, and the New Safe Medicines Faster Award.