“From Medical Biotechnology to Clinical Practice”

Report of a Workshop organised under the aegis of the
External Advisory Group (EAG) of
the Cell Factory Key Action

Quality of Life Programme
European Commission
Research Directorate General

Brussels, 8-9 June 2000

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Participating Organisations and Institutions

EFB European Federation of Biotechnology
EFPIA European Federation of Pharmaceutical Industries and Associations
EUFEPS European Federation of Pharmaceutical Sciences
EORTC European Organization for Research and Treatment of Cancer
ESACT European Society for Animal Cell Technology
ESGT European Society for Gene Therapy
ESCF European Society for Cystic Fibrosis
EURODIS European Organization for Rare Disorders
HUGO Human Genome Organization
ISAP International Society for Antiinfective Pharmacology
ICMR Italian Consortium for Medical Research
GENETHON

- Academic Hospital - Vrije Universiteit Brussel, B
- Institut Pasteur, F
- Imperial College, UK
- Istituto de Biologia Experimental e Tecnologia, P
- Istituto Scientifico H.S. San Raffaele, I
- Leiden Universiteit Medical Centre, NL
- St. Radboud University Hospital, NL
- The Royal Free Hospital and University College Medical School, UK
- Université Catholique de Louvain, B
- University of Essen, D
- University Hospital Ghent, B

- Novo Nordisk
- Roche Diagnostics
- Boehringer Manheim
- Pharmacia
- SmithKline Beecham
- Serono Pharmaceuticals
- Ingenasa, E
- Leibnitz Res Lab. For Biotechnology and Artificial Organs, D

- EMEA European Agency for the Evaluation of Medicinal Products

**EUROPEAN COMMISSION:**
- DG Research, Life Sciences Directorates
- JRC-ECVAM, Joint Research Centre - European Centre for Validation of Alternative Methods
EXECUTIVE SUMMARY

In the field of biomedical Research and Development, the pace of discovery and development of new diagnostic products, bio-medicines and therapeutic strategies are rapidly increasing. The approach taken in the U.S.A. reflects strong pharmaceutical competencies. Europe has to develop systems to facilitate further the path leading from discovery and development towards phase I/II clinical trials. This goal can only be achieved through the establishment of a more integrated network and tighter links between bio-technologists and clinical practitioners, while creating a more supportive attitude to innovation in bio-medicine by regulators and policy makers, at earlier stages in the development of products. This report summarises the findings of the workshop "From Medical Biotechnology to Clinical Practice", conducted under the aegis of the Cell Factory External Advisory Group (EAG). The purpose was to identify the bottlenecks that exist at the interface between the nascent medical bio-technologies and clinical practice, and to explore the opportunities to strengthen the competitiveness of the European bio-medical-development sector and health care industry.

Experts from five different constituencies put forward their views and identified, in a consensual manner, the major European bottlenecks under three main headings. These experts represented large pharmaceutical industry, Small and Medium Enterprises (SME) and university / clinical departments, patient-organisations, medical bio-technologists, clinical practitioners and regulators.

1. Integrated training and education - there is a dearth of experts able to manage and integrate different disciplines involved at the interface, from concept and development of medical biotechnology products, to clinical practice. This is true for both the more scientific aspects, dealing for instance with labile molecules (e.g. proteins) and their delivery or with complex tissues and organs, as well as for the technological and managerial components involved in development, testing and regulation.

2. Common facilities - there is a lack of reference health institutes, large human tissue banks, centralised clinical data banks, GMP facilities for early development as well as clinical facilities for conducting GCP trials;

3. Regulatory harmonisation requirements - different, non-aligned country rules for all steps from development to clinical trial and unclear national agency regulatory frameworks render development of new bio-medicines and European - wide trials very hard to perform.

Drawing from the information on the recognised bottlenecks, opportunities have been identified by the group to enrich and promote the pipeline of new European bio-medicines, relying partly on support from stronger networks of the academic sector, clinical departments, industry and regulators and on a joint effort towards harmonisation of reference practices, facilities and rules. A short list of specific recommendations was drawn from the discussion, directed to each one of the areas of opportunity.

The workshop participants urge the industry leaders, researchers and clinical practitioners, with the collaboration of governments and the European Union institutions, to address and act upon the issues raised in the report. This action may require mechanisms additional to those already in existence, but such mechanisms would strengthen the European Research Area concept put forward by Commissioner P. Busquin.
Table of Contents

Report

Agenda

List of participants

Proceedings
  - Abstracts
  - Overheads

Annexes
  Annex 1 – Information Available
    - A comment from individual EAG and HLEG members on Commission Communication « Towards a European Research Area »
    - Report from the Workshop « New safe medicines faster »
    - Work Programme of the Cell Factory key action

Annex 2 – List of EAG Cell Factory members
EAG CELL FACTORY Workshop
“From Medical Biotechnology to Clinical Practice”
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REPORT
Rationale and aims

As the results of the genomics revolution speed up, the pace of discovery and development of new diagnostics, biomedicines and therapeutic strategies is likely to increase significantly in the field of biomedical R&D. In order to face this challenge, a clear need emerges for an integrated approach by the relevant interested parties. More and more close co-operative interactions are needed amongst all the different protagonists driving medical progress, through the whole process from discovery to clinical practice: academic and research institutions, the private sector, from small biotechnology enterprises up to large pharmaceutical firms, clinical settings and patient associations, regulatory bodies, investors and policy makers.

A workshop, entitled “From Medical Biotechnology to Clinical Practice” and conducted under the aegis of the Cell Factory External Advisory Group (EAG), was organised to identify the bottlenecks that exist at the interface between the nascent medical biotechnologies and clinical practice, and to explore opportunities to strengthen the European bio-medical developments sector as well as health care industry competitiveness. It was felt that Europe had to develop systems to ease the path that leads from discovery and development towards phase I/II clinical trials in a way similar, but not necessarily identical, to what is being implemented in the USA. It was perceived that this goal could only be achieved through the establishment of tighter links between bio-technologists and clinical practitioners, while creating a more supportive attitude to innovation in biomedicine by regulators and policy makers. This requirement for an integrated approach defined the multi-facet profile of the participants in the workshop, which was conducted as a multi-lateral dialogue amongst academic and industrial medical research biotechnologists, clinical practitioners, patients associations and regulators.

Context

The Quality of Life and Management of Living Resources Programme is built around six Key Actions, targeted towards the policy objectives of enhancing the Quality of Life of the EU citizen and improving the competitiveness of European industry. The Cell Factory Key Action is specifically aiming at integrating innovative research and technologies and exploiting the outcome from this collaboration. Science of the highest international quality is an essential feature of the Work Programmes, but the outputs from research must be targeted to address the needs of society. In this way the full potential of the research findings can be realised in applications that benefit the entire European Community.

In the health care area, the Cell Factory Key Action dedicates a major effort to the integration of biomedical research and technological development to the exploitation of results. Indeed, several of the ongoing projects in the priority area “Improving the diagnostic and therapeutic arsenal for healthcare” follow the entire path from bio-medical discovery, through biotechnological development, to clinical implementation, with the aim to turn into reality the aphorism: “from bench to bedside.”
Amongst the protagonists of bio-medical development, the large pharmaceutical companies have already been able to bridge from medical biotechnology to clinical practice. The major outcomes have been produced outside Europe, particularly in the USA, because of its faster pace of translating innovation into practice. Several learned societies active in the field of bio-medical R&D, as well as medical and patient organisations (e.g. ESACT, ESGT, EFB, EUFEPS, EORTC, ISAP, EURORDIS¹ …) have also been fostering such a bridge. Regulators such as the EMEA¹ play an obvious and fundamental role for implementing the transfer from bio-medical discovery into clinical practice, through its role in the generation of guidelines, provision of scientific advice and the evaluation of dossiers submitted by the pharmaceutical industry. Finally, the European Commission Joint Research Centre (JRC) aims to provide a pivotal function of point of scientific reference in Europe.

The External Advisory Group of the Cell Factory Key Action (list of members and work-programme in annex) and the Commission services invited medical research biotechnologists, clinical practitioners, patients associations and regulators, involved at the interfaces between medical discovery, biotechnological development and clinical practice, to participate in the Workshop “From Medical Biotechnology to Clinical Practice”. Bottlenecks and opportunities throughout the whole process leading from discovery to new bio-medical developments were discussed and recommendations for improving this performance in Europe were formulated.

The areas of activity covered by the participants are not only at the forefront of the contributions to be obtained from Cell Factory projects in the health area, but also represent more generally a major potential, both social and economic, for European development and human quality of life improvement.

The structure and nature of this workshop, conducted as a constructive multi-lateral dialogue among all interested parties involved in bio-medical progress, as detailed further under bottlenecks/opportunities/recommendations, are well in line with the strategies supported by the “European Research Area”², conceived by Commissioner P. Busquin.

¹ Abbreviations: EFB (European Federation of Biotechnology), EMEA (European Agency for the Evaluation of Medicinal Products), ESACT(European Society for Animal Cell Technology), ESGT (European Society of Gene Therapy), EORTC (European Organization for Research and Treatment of Cancer), EUFEPS (European Federation of Pharmaceutical Sciences), EURORDIS (European Organization of Rare Disorders), ESCF (European Society of Cystic Fibrosis), ISAP (International Society of Antiinfective Pharmacology)
² more information available on: http://europa.eu.int/comm/research/area.html
Main Views Debated

Essentially, experts from five different constituencies (large pharma, SME\textsuperscript{3} and university/clinical departments, patient organisations, medical biotechnology and clinical practitioners, regulators) put forward their views, which were discussed by all and a general consensus obtained:

– The large pharmaceutical companies have been carrying out bridging from medical biotechnology to clinical practice for the last two decades. Nevertheless, the workshop attendees felt that there was a need to build bridges between SME’s and clinical departments, on one side, and the big industry on the other side to facilitate the transfer of technology from the former to the latter. Furthermore, large pharmaceutical companies would prefer to see more involvement of SMEs or even University/Clinical Departments, in the development of new candidate biopharmaceuticals, up to phase II clinical trials.

– The SME and university/clinical departments dealing with biopharmaceuticals for products or orphan drugs with smaller use have faced difficulties up to phase II clinical trials, in the recent past, in obtaining financial support for the jump from discovery to development, to cGMP\textsuperscript{2} production and on to clinical trials. Each of these steps has the potential to delay enormously the process and uses too many human resources in devising and creating solutions. Two other complaints relate to the lack of facilities and infrastructure for cGMP and GCP\textsuperscript{2} facilities as well as clear information and support to design all the different steps and trials along with adequate dialogue with competent regulatory authorities at a national level.

– The patient organisations made clear their urge and support for more candidate biopharmaceuticals to be developed and put into clinical trial since, in most cases, the alternative for patients may be early death or a very poor quality of life. Two further strong complaints were heard: the difficulty in carrying out multi-country clinical trials in Europe, with all sorts of different rules and procedures from the regulators involved, from ethical committees to national regulatory agencies, often more than one per country; a second difficulty relates to unbearable delays in the availability of new medicine approvals in some European countries.

– The medical biotechnology and clinical practitioners made clear their need for the existence of more practitioners, more infrastructure – possibly linked in some sort of loose, virtual network – for both cGMP production and GCP operation. Furthermore, for faster development, centralised databases and reference health institutes are required as well as access to large human tissue banks.

– The regulatory scene is dual; the EMEA has implemented a centralised process which has been invaluable in speeding up the evaluation and approval of new medicines. Unfortunately, the national scene is fraught with difficulties, with disparate actors, going from medical to ethical committees and passing through various agencies that are supposed to approve different steps in drug development but often do not have the experience and competence to do so. Furthermore, the contrast between the two European legal cultures – “not forbidden is approved” versus “not approved is forbidden” – creates serious difficulties. This situation is further complicated for the new ground breaking therapies – cell therapies, tissue and organ engineering – where rules of conduct are absent in most European countries. For gene therapy, steps have been taken in harmonising the regulatory requirements through the EMEA and perhaps this model should be used for the other new areas of technology cited.

\textsuperscript{3} Abbreviations: GCP: good clinical practices; GMP: good manufacturing practices; SME: small and medium enterprise
Bottlenecks

**Regulatory harmonisation**

- For new biotechnology products the review procedure has been harmonised and is undertaken in a given time period cited in the Regulations which set up the European Medicines Evaluation Agency. In addition, there are fast track facilities for the approval of products, provided there is sufficient justification. However, SMEs and Universities / clinical departments may not be aware of the regulatory requirements for the registration of medicinal products, thus steps should be taken to create fora where this information may be exchanged with the interested parties.

- There is a need for early dialogue between trial originators and authorities leading to clear-cut decision making processes for establishing different end points in clinical trials, which may allow faster answers to be obtained (e.g. cancer).

- There is a deficiency of common rules for developing and testing certain new bio-medicines in clinical trials throughout Europe. For newer areas such as tissue engineering, there is not only a lack of regulatory guidelines but also an absence of country regulatory authorities/agencies with clear-cut decision power to yield certificates for testing new modalities of biomedicines. For gene and cell therapies, steps have been taken in harmonising the regulatory requirements through the EMEA and perhaps this model should be extended to the other new technologies.

- It is extremely difficult to establish, throughout Europe, access to patients for clinical trials, specially needed for rare and orphan diseases. Different non-coherent country rules and lack of accurate information (or poor dissemination of the information), about which decision making authorities should be consulted in most countries, constitute the major bottlenecks.

- There is an unequal accessibility to the market for new medicines, in particular orphan drugs, in the European Countries. The fact that some medicines may be delayed in their approvals in some European Countries compared to others is essentially contrary to the European Union basic principles of single market.

**Common facilities – databases – references**

- It is difficult or impossible to access large human tissue banks needed for the development of new medicines.

- There is a need for European reference health institutes (similar, but not necessarily identical, to the USA National Institutes of Health, C.D.C.) and for centralised databases housing clinical data covering trial and post-approval phases. Such databases on clinical trials will be developed at EMEA once the Clinical Trial Directive has been put into force.

- There is still a dearth of training and facilities for cGMP, particularly for the production of small-scale material for clinical trials Phase I & II, which has a negative impact on the pipeline of candidate biopharmaceuticals which can be taken to the clinic.

- Similarly, there is a dearth of training and clinical facilities for conducting GCP, in particular for Phase II and rare diseases.

- There is a need to stimulate the use of in silico testing systems, together with developing better animal models and newer in vitro systems, in order to improve prediction of behaviour in humans.
Integrated training and education

- There are too few scientists able to integrate the different disciplines involved at the interface between medical biotechnology and clinical practice, i.e., able to manage the increased complexity of biopharmaceutical discovery, development and testing, as well as the transfer to large pharmaceutical companies or application for marketing authorisations.

- There are too few scientists and technologists capable of dealing with large, labile molecules like proteins, tissues and organs, as well as with cell and gene therapies, at all steps in drug development, delivery/application and regulatory levels.

Opportunities

- Stronger consortia of academia, clinical departments, industry and agency representatives will quickly improve the cultural attitude towards innovation and get new candidate products into Phase I/II clinical trials – this will be particularly useful for rare diseases and newer technologies, including tissue engineering, where large pharma may not take the lead.

- Starting earlier during the development of products and making it easier to initiate the dialogue between scientists and regulators is seen as an opportunity. A feasible way to reach this goal may be through the organisation of dedicated workshops.

- Closer involvement of bio- and medical- ethicists with scientists will improve dialogue with patient groups and improve perception of the European communities.

- Increasing scientific mobility and creating more effective joint appointment processes will further improve the transfer of the “tacit knowledge” required to integrate the interface between medical technology and clinical practice, industry, university and regulatory agencies. The creation of fora for multi-disciplinary discussions is also perceived as useful.

- Articulating and extending the limited existing competencies in GMP and GCP for cutting edge medicine technologies, as well as enlarging their delivery capacities, will create a “virtual” network enabling Europe to get more new, innovative biomedicines and tissue engineered products through clinical proof of concept.

- Familiarising and training more medical biotechnology scientists and developers in GMP and GCP data requirements will facilitate the widespread acceptance and use of reference practices.

- Establishing EU tissue banks will foster the development of medicines and technologies in the newer areas of medical biotechnology.

- Merging existing and in process clinical trial data as well as marketed drug data (adverse reaction observations) into public databases for clinical trials and organising patient databases will accelerate the development of new bio-pharmaceuticals and therapies.

- Reinforcing pharmacogenomics teaching and training, as well as creating integrated programmes for education and training in bio-medical research/development /management, will be an opportunity for both university and industry, as the integration between diagnostic, genotyping and therapy will keep increasing.
Recommendations

Multi-lateral dialogue (academy / industry / clinical departments / regulators / patients / ethicists / investors)

Stimulate further the prospective dialogue between regulators, academics and industrial scientists regarding new, cutting edge technologies at the early stages in the development of products. This could be implemented through several initiatives:

- creation of platforms to look into new biomedicine technologies,
- organization of workshops/fora for information and debate upon new biomedicines
- further stimulation of regulatory support to test and validate new biomedicine at an early stage of development
- support to networks among the multiple interested parties

Integrated (academy/industry/clinical departments/regulators) co-operation in R&D

Improve the co-operation from bench to bedside and feed experience back into development of future biomedicines, in order to assist transition from promising concept to pharmatype R&D:

• Provide quick and significant support for basic research operating in integrated consortia
• Improve conditions for Academy-SME collaboration in biomedicine development
• Support mobility and effective joint appointments between Academy, Industry and Regulators.
• Enlarge the involvement of clinical research in FP5 (clinical pharmacology, molecular pathology, molecular toxicology)
• Involve medical ethicists in laboratory work and stimulate exchange/mobility of experts in both fields.
• Increase focus on integrating in vivo / in vitro / in silico approaches and data

Harmonised regulations and reference practices

Create universal and well-known (-posted) rules for new bio-medicals test and approval as well as access to relevant authorities in each EU country:

• Harmonise clinical trial regulations across EU
• Improve the existing draft directive for GCP and extend the establishment and application of reference practices (GCP, GMP) to new areas
• Implement a pan-European, and world-wide approved, system of scientific and technological reference (GLP, GCP, GMP) for all the most relevant areas of bio-medical developments. In this respect, the established role of EMEA and JRC as centres of reference, in close collaboration with academies, industries and social players, should be reinforced.
Centralised shared data and material collections

Support the creation of centralised facilities, collections and data bases:

- Create a European registry for clinical trials, by merging existing and on-going clinical trial data, as well as marketed drug data (adverse reaction observations) into a public database – EMEA clinical trials database will be put in place
- Establish shared patient databases
- Establish a shared European tissue bank

Integrated training

Stimulate integrative and integrated training/education in bio-medical development, in order to adapt to the urgent need for most up-front scientific & technological competencies combined with advanced managerial skills:

- Contribute to training of physicians in drug development
- Create more opportunities to train scientists for and in SMEs
- Increase management training for dealing with the complexity of development and testing process and data
- Establish network of GMP/GCP facilities accessible to Academy and SME for training and preparation of biopharmaceuticals for Phase I/II clinical trials
- Support an integrated postgraduate training (Master, PhD) programme in “Medical and Pharmaceutical Research and Development” as a co-operation between academies and industries, in a network Organization.

“New safe medicines faster and for all”

Facilitate the rapid generation of novel, efficient, safe and easily accessible therapeutic and diagnostic tools:

- Stimulate faster and broader use of in silico trials
- Improve support to formulation and drug delivery strategies
- Increase support to development and testing of high-risk, often low-income, biomedicines up to phase I/II, especially for rare diseases and new medical biotechnologies not immediately supported by large pharma

It is interesting to note that the bottlenecks and recommendations hereby reported are complementary and synergistic to the conclusions drawn from a previous workshop entitled “New Safe Medicine faster” (Annex 1).
EAG CELL FACTORY Workshop
“From Medical Biotechnology to Clinical Practice”
Brussels, 8-9 June 2000

AGENDA
**Justification**

As the results of the genomics revolution, the pace of discovery and development of new biomedicines is likely to increase significantly. Europe, where cultural attitudes towards innovation differ from those prevalent in the USA, is lagging behind in the capacity to get new candidate products to Phase I/Phase II Clinical Trials. This situation can only be changed if many more links between research biotechnologists and clinical practitioners are established on the ground, at the same time as policy makers and regulators develop a more participative, partnering attitude to innovation in biomedicine.

**Aims**

This workshop will identify the bottlenecks and opportunities in working at the interface between the nascent medical biotechnologies and clinical practice. This workshop will also explore ways of fostering these opportunities to strengthen European clinical practice and healthcare industry competitiveness, in particular with a view to facilitate access to reliable, controlled and efficient Phase I/II clinical trials.

**Participation**

Participants would be medical biotechnology and clinical researchers (including participants to FP4 and FP5 projects) active at this critical interface in approximately equal numbers; a couple of regulators proactively involved in development of biomedicines will also be invited.

**Venue**

European Commission  
Avenue de Cortenberg 1, Brussels, Belgium  
Room 7 F

**Organising Committee:**  
Manuel Carrondo, IBET, ESACT, Cell Factory EAG  
Boerge Diderichsen, Novo Nordisk, Cell Factory EAG  
Elisabetta Balzi, European Commission, Cell Factory Unit

**Secretariat:**  
Hilde Somers, European Commission, Cell Factory Unit
Programme

8 June 2000, 14h – 18h30

Opening

Welcome and Introduction

- 14h00 – 14h15  European Commission – The Cell Factory Key Action
  Rainer Gerold, Director, Quality of Life and Management of Living Resources Programme
  Alfredo Aguilar Romanillos, Head of Unit, The Cell Factory Key Action

- 14h15 - 14h30  External Advisory Group - The Cell Factory Key Action
  Manuel Carrondo, EAG member

Session 1: Bottlenecks and Opportunities at the Interfaces
Medical Discovery / Biotechnology / Clinical Practice

Chairman: Olivier Danos, Génétique III, F and European Society for Gene Therapy

Opening Lecture

- 14h30 – 14h50  S. Donald, Center for Medicines Research International, UK

Industry statistics in clinical benchmarking: What does this tell us about the competitive environment.
Selected examples of ongoing experiences

- 15h00 – 15h10  P. Froguel, Institut Pasteur, F

Academic Consortiums for the Genomics Approaches of Frequent Diseases: the example of Diabetes

- 15h15 – 15h25  J. Weber, Imperial College, UK

Moving from the bench towards phase III: The example of Dextrin-2-Sulphate

- 15h30 – 15h40  C. Bordignon, Istituto Scientifico H.S. San Raffaele, I

The Italian experience developing biotechnology in gene and cell therapies

- 15h45 – 15h55  W. Sauerwein, University of Essen, D

Cancer Treatment by Boron Neutron Capture

- 16h00 – 16h10  A. Dodi, Anthony Nolan Bone Marrow Trust, UK

The Anthony Nolan Bone Marrow Trust: In house project developments and FP4-5 experiences

- 16h15 – 16h25  G. Leroux Roels, Univ. Hospital, Gent, B

Therapeutic vaccination for chronic viral diseases: from concept to clinic

16h30 – 16h40 Coffee Break

The input of pharmaceutical and biotech companies

- 16h45 – 16h55  M. Carrondo, IBET, P and European Society for Animal Cell Technology

Bridging cGMP biotechnological processes and clinical trials

- 17h00 – 17h10  A. Bader, Leibnitz Res. Lab. for Biotechnology and Artificial Organs, D

Technologies and clinical perspectives of cardiovascular tissue engineering

- 17h15 – 17h25  G. Draetta, Pharmacia Corp., S

(cancelled)

Mechanism-based cancer drug discovery: Implications for clinical development

- 17h30 – 17h40  T. Lund-Hansen, Novo-Nordisk, DK

How to get fast and easy access to GMP material for clinical testing

- 17h45 – 17h55  R. Rüger, Roche Diagnostics, D

Integrated Health Care Development from Research to Clinical Trial

- 18h00 – 18h10  I. Casal, Ingenasa, E

Vaccines production in insect cells

- 18h15 – 18h25  A. Bernard, Serono Pharmaceutical Research Institute, CH
**9 June 2000, 9h – 12h, 13h-16h**

**Session 2: Towards an integrated European breakthrough**
Chairman: Michael Browne, Smithkline Beecham, UK

**Views from pharmaceutical, medical and patient organizations**

- **9h00 – 9h15** G-J B. Van Ommen, *The Human Genome Organization*
  *The human genome project: medical implications, intellectual property rights and benefit sharing strategies.*

- **9h20 – 9h35** P. Tulkens, *International Society for Antiinfective Pharmacology*
  *Improving Antibiotic Therapy: a Paradigm of Fruitful Cooperation between the E.U., Local Regulatory Bodies, Academia and Industry*

- **9h40 – 9h55** N. Fabris, *Italian Consortium for Medical Research, I*
  *The site Management Organization (SMO) as a model to improve biotechnology/clinical research - Inter-Country collaborations to favour clinical-trials*

- **10h00 – 10h15** P. De Mulder, *European Organization for Research and Treatment of Cancer*
  *Development of immunotherapeutic approaches in cancer in a multi-centered and multinational setting*

  10h20 – 10h30 Coffee Break

- **10h35 – 10h50** A. Olauson, *European Organization for Rare Disorders*
  *Aspects from patients points of view*

- **10h55 – 11h10** J.A. Crommelin, *European Federation for Pharmaceutical Sciences*
  *The role of Academy in bringing biotech products to the market*

**Regulatory aspects**

- **11h15 – 11h30** S. Coecke, *European Center for Validation of Alternative Methods, JRC, EC*
  *EC/ECVAM validation strategies for newly developed technologies in toxicology*

- **11h35 – 11h50** J. Reden, *European Federation of Pharmaceutical Industries and Associations*
  *Impact of new technologies on regulatory requirements*

- **11h55 – 12h15** J. Purves, *European Medicinal Evaluation Agency*
  *Applications for marketing authorisations – evolution and opportunities*

  12h30 – 13h30 Lunch Break

13h30 – 14h30 **General Discussion**

14h30 – 15h30 **Wrap-up and recommendations**

- B. Diderichsen, EAG-KA3, M. Carrondo, EAG-KA3

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EAG CELL FACTORY Workshop

“From Medical Biotechnology to Clinical Practice”

Brussels, 8-9 June 2000
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ABSTRACTS
Industry Statistics in Clinical Benchmarking:  
What does this tell us about the competitive environment?

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The relative increase in pharmaceutical R&D expenditure compared with sales is putting the global pharmaceutical industry under pressure to improve efficiency while maintaining profitability. The industry must continue to improve output of high quality compounds by reducing development times, improving success rates and delivering sufficient numbers of high quality candidates into clinical development.

Data from CMR International’s databases containing information on key cycle times within drug development show that time savings have been made in development process in the late 1990s. These are most evident in the period from “compound code assigned” to “first human dose” and between “first submission” and “first launch”. Overall, time savings of around 20% have been made in activities completed in 1999 compared with 1994.

New technologies such as proteomics, combinatorial chemistry, chemoinformatics, high throughput screening, and industrialised screening applied to the drug discovery phases have been expected to result in an increase in the number of high quality compounds reaching the clinic. However, the annual number of compounds which went into man by 23 leading companies between 1994 and 1999 has remained static, suggesting that this increase has yet to occur.

In order to maximise returns on investment of a product companies are pursuing global strategies in the submission of regulatory dossiers to authorities world-wide. This is illustrated in the decrease in the average time between first human dose in Europe and the IND submission in the USA throughout the 1990s and the huge rise in patient numbers in an increasingly broad group of countries involved in clinical trials. Countries wishing to encourage the conduct of trials must have sufficient access to patients and high quality investigators, an infrastructure supporting the technology involved in contemporary trials and a reasonable regulatory demand.

Different regulatory processes between regions result in some significant differences in the time take for approval of products. For example, compounds assigned “priority” by the FDA in the USA take considerably less time to review by the FDA when compared with the European Centralise procedure.

In conclusion, three factors that must be addressed to allow the industry to react to current pressures are, an environment encouraging and supporting administration to man, global trials that are accepted world-wide and a consistent and transparent review system.
The European BNCT Centre in Petten: Organisational Structure

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Introduction

The first clinical trial in Europe of Boron Neutron Capture Therapy (BNCT) for the treatment of glioblastoma was opened in July 1997. The first patient was treated in October 1997 at the High Flux Reactor (HFR) in Petten, the Netherlands. BNCT is based on the ability of the isotope $^{10}$B to capture thermal neutrons and to disintegrate instantaneously producing two high Linear Energy Transfer (LET) particles, He and Li nuclei, with a high kinetic energy of about 2.5 MeV and a very short range in tissue of about 10 m $^{10}$B(n,$\gamma$)7Li. Such reactions, when produced selectively in tumour cells, opens an effective new modality for cancer treatment. In the late 1950's and early 1960's, BNCT trials were performed in the USA, but were effectively a failure[1,2]. Nevertheless, in the late 60's, Hatanaka in Japan demonstrated that BNCT does benefit patients[3]. However, the reported results were difficult to interpret, because the treatment was not carried out in a controlled manner. Nevertheless, the reported benefits stimulated a resurgence of BNCT activity both in the USA and Europe, leading to the start in 1994 of new trials at Brookhaven National Laboratory (BNL)[4] and Massachusetts Institute of Technology (MIT)[5], involving the treatment of glioblastoma (at BNL and MIT) and melanoma (at MIT). In Europe, effective research into introducing BNCT began in the late 1980's, following the injection of financial support from the Biomedicine and Health Research programme (BIOMED I) of the European Commission. This led recently, with further funding from the BIOMED II programme, to the start of a clinical trial of BNCT for glioblastoma multiforme. The trial is a Phase I study with the principal aim to establish the maximum tolerated radiation dose and the dose limiting toxicity under defined conditions. Regarding the dose limiting toxicity, the local radiation toxicity due to BNCT of the irradiated region of the patient's head and the systemic toxicity due to the drug sodium borocaptate (BSH) alone are to be detected [6]. It is the first time that a clinical application could be realised on a completely multinational scale, whereby a unique facility available for BNCT is localised in one country (The Netherlands) and is operated by an international team of experts under the leadership of a German radiotherapist, treating patients coming from different European countries. It has therefore been necessary to create a very specialised organisation and contractual structure with the support of administrations from different countries, who had to find and adapt solutions within existing laws that had never foreseen such a situation. Furthermore, due to the fact that a new drug, a new radiation beam and a new facility would be used, special efforts have been made on quality management, in order that the set-up at the facility and the personnel involved complied with similar practices in conventional radiotherapy departments. In this article, a description of the organisational structure and a more detailed description of the quality management aspects for the project are given.
Organisational structure and administrative obstacles

The project has been formulated such that 6 different hospitals from 5 different countries (Austria, France, Germany, Switzerland and The Netherlands) enter patients into the study. The treatment is performed by the Department of Radiotherapy of the University of Essen (Germany) at the HFR Petten, which is owned by the European Commission and located in The Netherlands. During the period of treatment, patients are hospitalised at the University/Academic Hospital "Vrije Universiteit" (AZVU) in Amsterdam. The study is carried out following an approved protocol of the European Organisation for Research and Treatment of Cancer (EORTC) BNCT Study Group[6]. The monitoring and data management of the trial are performed by the New Drug Development Office (NDDO) of the EORTC. The study is financed as a Shared Cost Action by the European Commission, within the BIOMED II Programme[7]. The treatment in Petten is carried out in co-operation with the Joint Research Centre (JRC) of the European Commission and the Netherlands Energy Research Foundation (ECN), under the overall clinical responsibility of the Department of Radiotherapy of the University of Essen which also provides the Medical Physicist. The co-operation of all these institutions, their different tasks and responsibilities are agreed by contract. The overall structure, indicating the principal functions and relevant responsible institutes, is shown in Figure 1.

Figure 1 : Organisational Structure for the BNCT Trials at Petten
(for abbreviations see footnote)4

To obtain approval for such a complex multi-national project was extremely difficult and time consuming. The initial application to the relevant national medical authority in the Netherlands was submitted in 1995. The complexity of the procedure was primarily due to the uncertainties in identifying the appropriate authorities in the Netherlands, as well as in the other European countries involved. Even the ministries themselves who deal with health policy, could not answer or identify the issues that had to be addressed and resolved clearly. No European approach is available due to the fact that medical applications fall under national law and that there is no harmonisation on the European level.

The issues which had to be solved are listed briefly here.

Reactor related:
- licensing of the reactor as a facility for patient treatment,
- licensing of the facility which is not part of a hospital to irradiate patients,
- gaining local approval on safety aspects, both nuclear and conventional, at the reactor site.

Protocol related:
- establishing the EORTC BNCT Study Group,

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4 SCA — Shared Cost Action
AZVU - Academisch Ziekenhuis Vrije Universiteit, Amsterdam
KFU - Karl-Franzens-Universität, Graz
ZKSJ - Zentralkrankenhaus St.-Jürgen-Straße, Bremen
LMU - Ludwig-Maximilians-Universität, München
CAL - Centre Antoine Lacassagne, Nice
CHUV - Centre Hospitalier Universitaire Vaudois, Lausanne
NDDO — New Drug Development Office
JRC — Joint Research Centre, European Commission
ICP-AES — Inductively Coupled Plasma - Atomic Emission Spectroscopy
ECN — Netherlands Energy Research Foundation
reconciling the different points of view of different ethics committees in different countries,
gaining approval of the study protocol by different review boards at different levels in a multitude of institutions,
handling a non-registered drug to be used in different countries following the study protocol,
regulating the execution of the study protocol as well as the operation of the facility by appropriate Standard Operating Procedures respecting the rules of Good Clinical Practice[8].

Patient related:

obtaining insurance for patients following different national procedures,
building up the local infrastructure for patient care, travel and nursing, including all anticipated emergencies.

Personnel and Institutional related:

licensing of foreign physicians (EU and non-EU) to treat patients in The Netherlands, being themselves staff members of a non-Dutch institution (Essen University, Germany),

enabling a non-Dutch Medical Physicist to be responsible and liable for Medical Physics at the HFR Petten,

identifying the different actions performed by persons coming from different institutions in different countries in order to establish and delineate the responsibility, and hence liability, towards the patient;

furthermore to describe the tasks of all participants, and to create and approve the appropriate agreements and contracts to define such structures,

applying the appropriate rules for radio-protection of the patients and the staff, respecting both German and Dutch regulations,

concluding contracts, subcontracts, associated contracts, collaboration agreements, etc. with all involved parties, following the rules established by the European Commission for Shared Cost Actions.

An overview of the agreements which had to be drawn up between the various parties is shown schematically in Figure 2, where the complexity of the interactions is more than apparent.

Figure 2 : Schematic Overview of the concluded inter-institutional contracts

Furthermore, in the Netherlands alone, the following governmental bodies (with Dutch abbreviations in brackets) had to be involved:

- Ministry of Health, Welfare and Sport (VWS)
- Ministry of Economic Affairs (EZ)
- Ministry of Social Affairs (SZW)
- Ministry of Environment (VROM)
- Ministry of Foreign Affairs (BZ)
- Central Ethics Committee on Medical Research (KEMO)
- Health Inspectorate for the province of North Holland
- Mayor's Office of the Community of Zijpe.

In the other countries, as well as on the European level, similar interactions were necessary without any possibility of co-ordination.
Conclusion

Despite the huge complexity of the organisation of the project, it is possible in Europe to carry out a multi-national cooperation in medical applications, which in itself is a demonstration that it is possible to introduce ways to use unique, highly sophisticated, expensive facilities in Europe. Furthermore, the different laws and requirements between the countries involved, which resulted in an unnecessary delays in the start of the trial, emphasises in itself that a real harmonisation within Europe would be a tremendous help in future multi-national trials.

Acknowledgement

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References

The Anthony Nolan Experience: In house Patenting and Commercialisation, and our FP4 and FP5 experience.

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The Anthony Nolan Bone Marrow Trust is the single largest independent Bone marrow registry in the world. It holds data on approximately 300,000 marrow donors. It provides donors world wide. The patient data base therefore represents a unique set of reference data for HLA analysis and monitoring of patients pre and post Bone marrow transplantation and for sequential post transplant follow up.

The goals of the Institute are to improve the matching for Bone marrow transplantation, to develop immunotherapy and monitoring for viral infections occurring post transplant, and the investigation of the pathogenesis of different leukaemia's i.e. CML, AML and EBV driven malignancies such as Hodgkin's disease. We have developed patented and marketed a technique for improved HLA typing with the ability to resolve up to 1 base pair difference in similar HLA alleles. This technique is called RSCA (Reference Strand Conformational Analysis). It is an ideal technique for fast through put HLA typing and for donor selection. We are now developing this for T cell receptor Vβ analysis.

The patenting and development of this technique was performed totally in house and has been a valuable lesson for us in the operation of the various administrative hurdles that have to be achieved prior to having a marketable product. Marketing proved more of a problem and despite having a functional operational product we could not market it through a UK or EU company and eventually went to an American company who have funded us to develop this product to market and it will be released in the fall of 2000. In order to circumvent this type of setback, a data base of companies and the types of products that they would be willing to consider for sponsorship in terms of marketing might be a useful adjunct to the pre-application work-up.

Through our involvement in immunotherapy we became successful partners in a European FP project investigating the requirements for the production and use of dendritic cells for the in vitro priming of anti peptide responses to tumour related antigens (EUCAPS). We were also partners in a program examining the use of cord blood as a source of stem cells for transplantation. Our laboratory has initiated the in house production of Class I and II tetramers which we are using to monitor patients with CMV viraemia post transplantation and also to monitor levels of minor antigen reactive cells in transplant patients.

The positive lessons that we have learnt from our FP4 /5 interactions are issues related to instigation of new technologies such as immunotherapy where GMP production of cells and reagents for administration to patients is important. What appears to be a bottleneck in this area is the lack of experienced hospital based centres that have set up their own GMP facilities and have gone through the various regulatory steps in order to conform to the legal and ethical requirements needed. Many of the large pharma companies have experience in some of these areas and the setting up of a register of individuals willing to act as guides either by physically hosting visitors for short periods or by providing advice might speed up the process of bringing some of these new technologies to the fore on a wider scale.

We feel that it is important for this work to be continued within a EU framework with the involvement of centres within Europe because of the clinical and commercial benefits that may underlie collaborative group findings.
Therapeutic vaccination for chronic hepatitis B and hepatitis C infections: from concept to clinic.

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Chronic infections with the hepatitis B virus (HBV) and the hepatitis C virus (HCV) represent a serious, global health problem. The WHO estimates the number of people chronically infected with HBV and HCV at 350 million and 150 million, respectively. These chronic infections respond poorly to antiviral therapies (interferon and/or lamivudine for HBV and interferon with or without ribavirin for HCV). The high failure rate, the numerous side effects and the high cost of standard antiviral therapies together with new insights in the pathogenesis of chronicity have fueled the search for alternative strategies to combat these chronic infections. It has been repetitively observed that patients who suffer from a chronic HBV or HCV infection display a weak and oligoclonal or no T cell response at all to structural and non-structural proteins of these viruses, whereas patients that clear the virus spontaneously usually have strong and polyclonal antiviral T cell responses. These observations have led to the speculation that chronic HBV or HCV infections might be treated by stimulating the patients’ immune system with a single or a combination of selected viral antigens. This stimulation primarily targets the cellular arm of the immune response (helper and the cytotoxic T cells) and to a lesser extent the humoral arm (antibody production).

In the past decade several academia- and industry-based research groups have directed their efforts on the development of therapeutic vaccines for HBV and HCV. A variety of antigen preparations has been produced (proteins, peptides, lipopeptide, HBsAg-anti-HBs immune complexes, DNA vaccines, viral vectors, ..) and different adjuvant systems (aluminum salts, monophosphoryl lipid A, Quillaria Saponaria or QS21, ..) are being evaluated. Pilot studies of vaccinotherapy in chronic HBV infections have shown encouraging results and a first evaluation of a candidate HCV is soon to start.

Several factors make the development of a therapeutic vaccine for HBV or HCV a cumbersome, costly and time consuming process and the road from concept to clinic turns out to be ‘long and winding’. Some factors are purely scientific whereas others are more of a practical and/or logistic nature. Despite the growing insight in the immune pathogenesis of chronic HBV and HCV infections the ultimate cause(s) for the viral persistence remain(s) unknown. Today’s immunotherapeutic strategies may therefore target the wrong antigen(s) and trigger inadequate or even undesired immune responses. More research on the mechanisms of viral persistence should ultimately lead to the key information needed for the design of the ultimate therapeutic vaccine.

Another factor that complicates the study of therapeutic vaccines for chronic HBV and HCV infections is the lack of easily accessible and affordable animal models. Models for chronic HBV are the woodchuck, the Peking duck and the chimpanzee, whereas for HCV only the chimp can be used. Transgenic mice carrying the full-length HBV virus or expressing selected regions of HBV or HCV are useful experimental tools but are not really suited for the study of therapeutic vaccines because of the immunological tolerance to the target antigens that is inherent to transgenes. Small animal models for acute and chronic HBV and HCV infections are badly needed and would undoubtedly promote the development of novel antiviral therapies.
Bridging cGMP Biotechnological Processes and Clinical Trials

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Past the level of discovery, three steps may be considered prior to large-scale trials: product development, cGMP production and clinical trials for phases I and II. Although different bottlenecks and opportunities exist for each, an integrative approach to these three steps is essential to reduce time-to-market and cost of product within the best quality levels required for human medicines.

At IBET, we have experience with different types of recombinant proteins, including fusion proteins, and some virus like particles both for therapeutics, diagnostics and vaccine utilisation as well as for retrovirus and DNA for gene therapy; in the context of this workshop, biopharmaceutical medicines should also embrace cell therapies and tissue engineering including “artificial” organs. Compared to the current small molecule pharmaceuticals, a key difference constituting a bottleneck is that there is, as yet, not possible to depict predictive models for the development phase (from bioproduction down to final purification); although past experience comes very handy in devising a preliminary, integrated production process. Nevertheless, to increase the opportunities one should produce “learning” models as soon as sufficient data is obtained such that the “hindsight” that such models yield will permit a reduction in the number of development tests. In order to further facilitate stepping up to cGMP, such Process System Engineering developmental tools need to be coupled to the development of robust Process Analytics.

At the cGMP level, as a candidate product gets closer to Phase I and II, sliding standards need to be established that will grow in complexity up to the production phases III and IV; in particular, demands regarding information technology validation and raw materials testing (from bona fide vendors) need to be relaxed at phase I/II. This attitude requires earlier regulatory agency involvement, so the regulatory requirements evolve in paralell with technology advances. This cooperation is even more necessary for newer biomedicines, eg. organs and cell and gene therapies

The entrance into clinical trials for phase I/II controls the whole integrative process. Indeed, anticipating issues like regulatory requirements, quality needs ranges for preliminary dose delivery routes and formulation feeds backward the two earlier steps of development and cGMP production. There is thus a requirement for more hospital units to develop Good Clinical Practice competencies (GCP) and interface capabilities.

The drive to go earlier into man, to permit feedback into discovery, will further require the integrative outlook and management of these three steps of development, cGMP product and clinical trials – possibly justifying that more physicians can create a good interface into drug development.

This integrative approach reviewed here is well established at the large pharmaceutical companies. But the much larger needs in the post-genomic era now opening up, yielding many more lead compounds and candidate products, many of which will not be of immediate interest to the large pharma companies and thus should be developed by European start-ups and SME’s identifies a strong opportunity to reinforce all three types of infrastructure (development, cGMP and GCP phases I/II) and to train people in an holistic way from gene to product, from developers to clinicians including regulators.
Disorders of cardiac valves cause significant morbidity and mortality. These disorders affect persons of all ages and can result from congenital or degenerative conditions as well as from infections. Treatment often necessitates replacement of the defective tissue and replacement by a mechanical or bioprosthetic valve following glutaraldehyde fixation. Disadvantages of mechanical valves include life long anticoagulation. Bioprosthetic valves initially approximate the hemodynamic properties of the natural valve but carry a significant risk of calcification, which has an incidence of 40-50% in children at 4 years.

The aim of the present study was therefore to develop a human bioartificial heart valve / vessel technology. For this aim a xenogeneic acellularied starter matrix is repopulated with cells of the valve recipient to ensure regeneration during long - term in vivo use. For this purpose, porcine aortic valves were treated enzymatically to remove cells. Resulting structures were analyzed histochemically, by scanning and transmission electron microscopy to study the integrity of the remaining 3-D matrix. This matrix was then seeded using endothelial cells and myofibroblasts. Preclinical trials have been initiated.

The results demonstrate that it is possible to almost fully remove cells from cardiac valves without major structural damage under in vitro conditions. This fully biologic matrix could consecutively be sterilized and re-seeded by autologous vascular cells. In vivo implantation in a growing sheep model indicate growth, assimilation and regeneration capacity.

Conclusion: This concept leads to the in vitro engineering of a human cardiac valve using allogeneic or xenogeneic matrix potentially capable of regeneration.
How to get fast and easy access to GMP material for clinical testing?

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There are currently lots of biopharmaceutical projects in the EU as a result of the increased discovery effort within biotechnology. However, to test these new opportunities in humans, you need to get GMP qualified material available for clinical testing. This seems to be a real bottleneck in the EU. The facilities needed depend on the specific projects but may include fermentation facilities for prokaryotic cell, facilities for mammalian cell growth or facilities to produce transgenic plant or animals. Only few commercial facilities are available and to very high costs. Further, people with proper training are a scarce resource.

To solve this problem two actions plans are suggested. Either the EU could build up a European Biopharmaceutical Production Centre or add GMP facilities to current centres at universities in Europe. This would so to speak create a virtual centre. The real or the virtual centre should have two tasks: to build up expertise within pilot GMP production and to serve SMEs and European institutions as a proactive vendor of GMP qualified biopharmaceuticals for clinical testing. The benefit of the project to the European Citizen will more, innovative biopharmaceuticals, more biotech jobs and an increased global competitiveness.
Integrated Health Care Development from Research to Clinical Trial

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The combination of diagnostic tests and specific treatments is frequently the basis of improved treatment strategies. This applies to many disease areas like viral load analysis in viral infections, glucose measurement in diabetes or exact tumor staging in oncology. Roche has established an Integrated Health Care Solution (IHCS) Unit, which is developing such combinations in collaboration with the divisions in Diagnostics and Pharmaceuticals concerned with the according disease area. IHCS activities are aiming at predisposition, targeted screening, prevention, diagnosis as well as treatment and disease monitoring. The scope of IHCS activities reaches from utilizing genomics technologies for marker and test development to testing new diagnostic tools within clinical trials to bringing combined diagnostic and pharmaceutical products to our customers. This integrated approach will bring benefit to patients, doctors and public health services.
Vaccine production in insect cells

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Insect cells are being used for over a decade for the expression and production at high level of potential vaccine candidates. The final commercialization of these products has been hampered till now by several factors: lack of knowledge of the baculovirus expression system, culture and recovery conditions for medium and large scale cultures of insect cells, costs of the assessment of vaccine efficacy and safety and, finally, the burden and complexity of the regulatory affairs to get the registration of a recombinant vaccine. These factors, together with the high expenditures, have become major bottlenecks especially for SMEs in the development of new improved vaccines. The production of porcine parvovirus (PPV) virus-like particles (VLPs) has been selected as "proof-of-the-concept" system in order to solve these problems. PPV is responsible for a major reproductive disease in pigs, which is usually controlled by vaccination. The objective of this project is to bring for the first time a process of vaccine production based on the expression of recombinant VLPs in insect cells close to the market. It is expected that results achieved in this project will allow for a rapid progress in the registration and commercialization of this and other baculovirus-derived recombinant vaccines, which will pave the way to a new generation of safer and more economical vaccines.
Pharmaceutical development: current issues and perspectives

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In this presentation, I will review the key issues of drug development in the pharmaceutical industry today and tentatively highlight the short term and long term perspectives of this activity. The presentation is organised into three parts: 1) how drug development needs a better integration with the discovery phase, 2) how to deal with the fact that a significant proportion of discovery events occur in the clinic and 3) how to implement and best use the new technologies such as pharmacogenomics, e-biology which orients the market towards individual health care.

Drug development efficiency has to improve to reduce fall-out rate from the first injection into man to the launch of a successful drug. It is important to analyse why compounds fail and why they succeed and this can be greatly facilitated by a well designed knowledge transfer. In order to achieve this objective, the current trend in drug development is to carry out some key activities earlier in the process, closer to discovery. Clinicians and professional “developers” provide their input into the discovery project decisions and, vice-versa, the discovery teams are also exposed to development issues.

Drug discovery has also to integrate with the clinic as 50% of the top 50 drugs were not developed for their final indication (D. Brown, Research Director, Roche Discovery). The best and most recent example is sildenafil (Viagra), a PDE5 inhibitor originally developed as anti-hypertensive and which is now a blockbuster drug indicated for erectile dysfunction. On the contrary, some clinical observations are quite difficult to model in-vitro. One example of this problem is growth hormone (Serostim) which, when prescribed to cachectic AIDS patients, is associated with improvements in strength, quality of life, fewer opportunistic infections and improved survival in good responders. However, the effects of growth hormone on stimulation of protein synthesis in L6 muscle cells cultured in-vitro are non-significant.

The recent progresses made in pharmacogenomics are changing the overall approach to drug development. The information provided by the “genome technologies” are key for pharmaceutical development for several reasons: several independent alleles can cause the same disease in different individuals; a given drug usually targets only one allele, hence all patients not carrying this allele may be non-responders; gene polymorphism, in particular that of the P450 enzymes affects drug metabolism (efficacy, toxicity,…); and finally the combination of a particular drug with a particular allele variant may cause side effects. There are clear reported examples of the impact of allelic variation on metabolism of a drug, absence of or poor response to it, or resistance to a disease. This information is at the tip of our fingers right now that the technology is mature enough and e-biology must be considered as an integral, essential tool for the development of future drugs.
The Human Genome Project: medical implications, intellectual property rights and benefit sharing strategies

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The Human Genome Project, the mapping of our 100,000 genes and the sequencing of all of our DNA, will have major impact on biomedical research and the whole of therapeutic and preventive health care. The tracing of genetic diseases to their molecular causes is rapidly expanding diagnostic and preventive options. The increased insights into molecular pathways, gained from high throughput "functional genomics", using DNA- and protein-chip approaches and specially-designed animal model systems, will open great perspective for pharmacological and genetic therapies. Powerful bioinformatics and biostatistics will further improve our pattern recognition and accelerate progress. A rapidly expanding area of high expectations is that of "pharmacogenomics": The design of more effective drugs with lower toxicity, through tailoring of drug treatment to individual, genetically-determined differences in drug metabolism. Not only will this reduce the cost of health care through decrease of adverse drug reactions, but a better stratification of populations will also provide more statistical power more upstream in drug trials. However, the optimal benefits from the current explosion of 'data mining' will only be realised when the basic data are made and kept publicly accessible, while at the same time safeguarding the protection of intellectual property arising from downstream inventions. This is one of the goals of HUGO, the international Human Genome Organisation, established 10 years ago to assist coordinating data acquisition and exchange and societal implementation of the genome project. Additional points of attention in this historic endeavour are the prevention of stigmatisation and discrimination and the safeguarding of a worldwide balance in the contribution by - and benefits to - different populations, while respecting the diversity in cultures and traditions.
The SMC-SMO-JPF Model for "Cycle Innovation"

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The "Cycle of Innovation" of new biotechnological entity (NBE), as for other sectors in the pharmaceutical area, shows in Europe two major phases: a relatively good scientific basic research and a weak process development, that does not result in a competitive market.

This second issue depends, rather than on synthesis and pharmacology of NBE, on environmental factors such as economical evaluation (cost of good, selling price, reimbursability, competitors etc.) and human factors (ethical/moral prejudices, conservative medical cultures, popular habits etc.) and on clinical researches.

These factors, particularly the cost of clinical researches, that may account for as much as 60-70% of the total cost, may give an advantage to the companies able for big investments. Delay in reaching the break-even and reduction of the gross profit may prevent the majority of potential NBE to reach the market (out of 100 potential NBE not more than 1 or 2 entities reach the market). This is obviously more evident for orphan drugs, where besides the difficulties reported above, there is the additional factor of the small market.

Solutions have been tried in order to reduce the cost of clinical trials. The traditional process requires to the sponsor to organise the management of the clinical research using various investigation sites or alternatively to engage a Contract Research Organisation (CRO).

In spite of the increase in the last years of the market for contract study conduct requests (+ 16% annually), neither the annual (- 6%) reduction of the review time nor the increment of outsourcing and of streamlining operations have improved the clinical developmental process.

An alternative process has been recently proposed using the "Site Management Organisation" (SMO). This consists in a business enterprise among hospitals and research centres with multiple study conduct locations (regional or national, but international or inter-regional are possible as well), that are managed centrally by a corporate structure. SMO is focused on providing two primary assets - a large and diverse group of physicians and patients, and clinical study data treated more systematically.

Central research operations, standard contracts and operating procedures, new technology to manage information and the streamlining approval times give to SMO the advantage to reduce costs and time and to offer competitive pricing, while increasing quality.

Such advantages may certainly reduce the bottleneck between basic research and the market and may apply to big and small companies. Nevertheless, reducing of cost using SMO may still not be sufficient to favour drug development by Small-Medium-Companies (SMCs) and to favour potential NBEs to reach the market.

Here, we propose a model of drug developmental process, called SMC-SMO-JPF (SMC-SMO Joint Project Financing), that, in our opinion, might overcome these problems. The model is based on the following considerations:

a) the great part of the clinical cost is actually due to human resources in clinical settings;

b) generally clinical research represents a useful, but not an essential income for clinicians;

c) clinical investigators, and their institutions, become financial supporters of the drug development process, accepting a switch from an immediate return to a long term payment through royalties;

d) the SMO has the business organisation to support the matter;

e) the European Community (E.C.) may favour the SMC-SMO-JPF and also promote "business angels" to participate to the joint venture, particularly for the start-up;
The SMC-SMO-JPF has the following advantages:
- economical risk is modest for SMO and costs are lower for SMCs;
- the model promotes interaction between Industry and Academics in a more efficient way, favouring development of research on NBE;
- gives an advantage for the population, by favouring development of drugs for orphan pathologies;
- gives to SMCs the opportunity for develop their own products;
- gives to the E.C. the opportunity of promoting transfer from biotechnology to clinical practice through SMCs-SMO joint-venture at inter-regional (eventually inter-country) level.
Development of immunotherapeutic approaches in cancer in a multi-centered and multi-national setting

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EORTC Board Member

The present strategies against cancer encompass prevention, early detection followed by local treatment consisting of surgery and or radiotherapy, and in case of systemic disease by chemotherapy, hormonal therapy and bio-immunotherapy most frequently combined with the early mentioned local approaches. The classical development of cytotoxic agents based on preclinical data through phase I, II and finally phase III is well established and accepted. The ultimate goal of most treatment interventions is cure but reality forces us to accept prolongation of survival and eventually progression free survival as valid endpoints. Other options are objective measurable response quality of life and certain health economic issues. The more recent approaches such as bio immunotherapy do encounter major problems, which will be discussed below. This new approach makes use of the increased knowledge on malignant growth and the complex interaction between tumor and host. Examples are immunotherapy, several forms of inhibition of metastases and angiogenesis, growth factor receptors, etc. The development of this class of agents is different compared with the above mentioned approach for cytotoxic agents as can be best demonstrated with the application of vaccination strategies in the treatment of cancer. The ultimate goal is similar but unlikely to be achieved in far advanced disease. Next to clinical signs of activity such as objective tumor response proof of concept is important i.e. sero conversion as a sign of induced humoral anti tumor activity and or an increase in the frequency of tumor specific cytotoxic T cells. This proof of concept can be considered as a surrogate endpoint in vaccination trials but requires specific laboratory expertise and is not generally accepted as a valid trial endpoint. Early studies (phase I studies) will aim at toxicity and the optimal immunological response. Pending the antigen the approach is either antigen specific such as mage 1 in melanoma, head and neck cancer and bladder cancer or disease specific such as melanoma or colorectal cancer. Another problem is the compromised immune competence in patients with advanced cancer, which may obscure relevant activity in less advanced disease. Potential tumor vaccines are: peptides, proteins, relevant DNA sequences incorporated in viral or bacterial vectors, naked DNA, gene transfected cell lines or autologous tumor cells etc. Organizational problems related with this approach are the following: patent issues, complicated and per country varying approval procedures before a study can be initiated, availability of specific clinical and laboratory expertise, specific clinical environment in vace of the use of viral and bacterial vectors, insurance and liability issues and unclear requirements for registration. Close collaboration is needed between basic researchers, clinicians, pharmaceutical companies and regulatory authorities. Challenges are: [1] Validation of clinical trial methodology such as validation of biological surrogate endpoints, the development of statistical methodology based on validated surrogate endpoints and vertical development of cancer vaccines based on translational endpoints correlating to clinical meaningful endpoints. [2] Absolute need to perform the above to gain public/scientific visibility and credibility. [3] Absolute need to support such European platform by academics and European authorities (support). [4] Need for education of regulatory agencies striving for supra national procedures, of ethics committees who are unprepared to face unusual protocols and unclear understanding of methodology and the selected patient populations, of medical professionals to ensure adequate trial execution and the public for a clear visibility of the goals and possible outcome.
Several stages in the evolution of new test methods have been identified: research, test
development, prevalidation, and validation, independent assessment, regulatory acceptance and
routine implementation (Balls et al., 1995).

To facilitate this process, ECVAM interacts and co-operates with other institutions and other
services of the European Commission, and is often practically involved in various stages toward
regulatory acceptance, including the research and test development phases, as well as
prevalidation and validation.

A clear illustration of the successful collaborations between the EU actors is given by the recent
acceptance of three scientifically validated non-animal test methods for topical toxicity testing,
e.g., two methods for corrosivity testing and one for phototoxicity testing. The three methods
were accepted by the Competent Authorities of the 15 EU Member States at the 27th Meeting of
the Committee for Adaptation to Technical Progress of Directive 67/548/EEC on the
Classification, Packaging and Labelling of Dangerous Substances. The three methods are the
Transcutaneous Electrical Resistance (TER) procedure and the EPISKIN™ reconstituted human
skin test, which are now part of Annex V method B.40. Skin Corrosion, and method B.41. 3T3
NRU Phototoxicity Test. Guidelines similar to those presented to the Committee for Adaptation
to Technical Progress of Directive 67/548/EEC were sent to the OECD Secretariat, and are now
under consideration by OECD Member Countries. It is therefore hoped that the three methods
will soon achieve world-wide acceptance via the OECD.

In ECVAM’s work on the prevalidation and validation of in vitro test methods, it became
apparent that the acceptance of validated in vitro test systems by regulatory authorities would be
facilitated by adherence to the principles of Good Laboratory Practice (GLP). A workshop on the
OECD GLP principles applied to in vitro studies was therefore organised by ECVAM on 6-9
December 1998, in Angera, Italy. The workshop participants came from academic, industrial and
administrative backgrounds in in vivo and in vitro toxicology, the application of GLP, and/or
quality assurance systems. The report and recommendations of the workshop were published in
ATLA (Cooper-Hannan et al., 1999). In the report, the OECD principles of GLP are presented in
tabular form, with the additions and modifications necessary for in vitro studies. The document
has been forwarded by the European Commission to the OECD for review by the OECD GLP
working groups.

In anticipation of the fact that the implementation of GLP in an in vitro facility could be an
expensive, time-consuming and difficult process, a GLP on-line in vitro toxicology Management
Information System (OLIVE®JRC) has been developed at ECVAM to assist in applying the GLP
process in an in vitro environment (Coecke & Bowe, 1999). OLIVE®JRC will be presented as a
final package, which can be accessed either from the internet, intranet, or as a stand-alone
system. It consists of databases for the day-to-day running of the laboratories, covering all
aspects of GLP, basic documentation and the manuals necessary for an in vitro toxicology
laboratory, and specific standard operating procedures, quality procedures and administration
practices. High priorities for OLIVE®JRC in the ECVAM in vitro GLP policy are user
friendliness, increased efficiency of data management, easy information flow, and minimisation
of costs, paperwork and use of human resources making GLP more accessible to smaller in vitro
laboratories world-wide. The system will be available world-wide, with the aim of facilitating
the submission of in vitro toxicological data and facilitating the acceptance of validated in vitro
test systems by regulatory authorities.
New challenges are arriving in the field of systemic toxicity. To ensure relevance to the in vivo situation in this mechanistically more complex field, the in vitro approach has stimulated the use of advanced methodologies employed in new hazard assessment strategies. This leads to the development of novel human-based, but also individual-based, test-models.

An illustration of ECVAM’s strategy in stimulating the wider use and regulatory acceptance of new advanced methods in systemic toxicity testing (target organ toxicity, target system toxicity, carcinogenicity, etc.) is ECVAM’s laboratory work and associated established European networks. The laboratory studies at ECVAM are focused on elucidating pharmaco-toxicological mechanisms, test development, and the prevalidation and validation of advanced tests and technologies in the following areas: metabolism, characterisation and use of genetically engineered mammalian cell lines harbouring mainly human drug metabolising enzymes for studies of metabolism-mediated toxicity, metabolic stability, induction, inhibition, human drug polymorphism, co-culture applications and chronic toxicity; development of medium throughput metabolism screening systems (Coecke et al., 1999); neurotoxicity, key mechanisms of neuropharmaco-toxicological processes at the molecular and cellular levels, to provide early biomarkers of exposure, effect and susceptibility for use in designing advanced biotechnological test methods for evaluating neurotoxicological hazard (Stingele et al., 1999); embryotoxicity with genetically engineered embryonic stem cell lines (Bremer et al., 1999); haematotoxicity, especially with regard to anti-cancer drugs (Gribaldo et al., 1996); metal toxicity (Migliore et al, 1999); identification and evaluation of new endpoints for use in an in vitro nephrotoxicity screening test applicable to other in vitro epithelial barrier systems (Prieto, 2000); development of new technologies and approaches for long-term toxicity testing.

The ultimate systemic toxicity of a chemical in vivo is strongly influenced by the time-dependent processes of intake, uptake (absorption), distribution, biotransformation and elimination. These factors determine the biokinetics (toxicokinetics) of a compound in a particular species. Ways must be found of evaluating such factors, so that they can be taken into account when predictions of in vivo toxicity are based on in vitro data. Therefore, it will be essential to design an integrated testing strategy for detecting systemic toxicity, which incorporates various appropriate in vitro and computer-based models, including biokinetic models.

A demonstration of success at a more complex level of toxicity can already be shown. On the 14th of March it was agreed that the ECVAM funded international validation study on three embryotoxicity tests had been successful. In this study, a total of twelve European laboratories were involved, including ECVAM. The three methods are the whole rat embryo culture, the micromass culture and the embryonic stem cell methods (Genschow et al., 2000).

The successful skin corrosivity and phototoxicity validation studies are also significant in other ways. Firstly, they give support to the value of the principles of validation agreed at the ECVAM workshop on practical validation, held at Amden, Switzerland, in 1995 (Balls et al., 1995). In addition, they confirm the value of the ECVAM prevalidation scheme and the importance of the proper definition, validation and application of prediction models. Finally, a great deal has been learned about the road to regulatory acceptance of validated non-animal test methods. A precedent has been set, and it is to be hoped that this road will be less full of potholes and will be traversed more quickly in the future.

“Human(e)” science leads to better science, due to a more-detailed understanding of the interference of endogenous and exogenous substances with specific biological processes as they occur in humans. Scientific collaborative networks, biotechnology platforms and human and individual-based integrated testing strategies are therefore the only ways forward for adequately screening and labelling the large numbers of chemicals already on the market and providing in the near future accepted in vitro tests for systemic toxicity.
References


The impact of new technologies on research and development of medicines

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Basically two aspects determine modern pharmaceutical R+D:
the enormous opportunities provided by the technological and methodological break-throughs of
the last decade and the challenges imposed by increasing R+D costs and price control and other
health policy measures.
The key role of biotechnology in the revolution of biomedical research is obvious. However, the
contribution of other technologies such as information technology, miniaturisation, automation
e tc. should not be underestimated.
The new technologies had tremendous impact on the discovery processes for new medicines,
whereas until recently only few changes have occured in the way that preclinical and clinical
drug development are performed. Drug development, being the most time and resources
consuming process is now the focus of big efforts of the pharmaceutical industry to make it
faster and better.
Preclinical efficacy and safety assessment strategies to support fast tracking into humans are
undergoing significant changes driven by advances in molecular biology and more mechanistic
understanding of drug action. High-throughput tests to predict animal toxicity and human
adverse reactions and in-silico and in-vitro screens to evaluate ADME parameters and to study
the relationship between pharmacokinetics and pharmacodynamics are being developed.
Clinical trial simulation and modelling and the development of biomedical markers and
meaningful surrogate end-points are contributing to a new way of planning and evaluating
clinical trials.
Pharmaceutical companies are increasing their investments in the emerging discipline of
pharmacogenomics – the study of genotype and its relationship to drug action. Genomics offers
the prospect of a more precise, efficient, and predictable clinical development process and it may
lead at the end to a redefinition of thera-peutic markets.
Gene Therapy is a new disease treatment based on DNA technology which has made substantial
progress. However, further technology development is required to assess preclinical safety and
efficacy and to define and validate clinical end-points. An appropriate adjustment of regulatory
requirements is urgently required.
The impact of emerging technologies on discovery and development of new medicines is
obvious. As a consequence a paradigm shift in regulatory requirements for the approval of new
medicines and therapeutic approaches is required. This is evident in particular for gene and cell
therapy and borderline approaches involving medicinal products / medical devices / engineered
tissues and others. A continuous dialogue between and joint efforts of regulators, academics and
pharmaceutical industry is required in order to keep pace with the technological development
and in its application in health care.
We have to realize that the great potential of the new technologies in the health care sector can
not be exploited if there is no public acceptance. Safety and ethical concerns have to be taken
seriously and all attempts need to be made to inform and educate the public on benefits and risks
of new technologies. Perceived risks are just as real as real ones!
Finally new types of medicinal products, new therapeutic approaches and diagnostic possibilities
will result in a redefinition of the markets. "Personalized medicines " will have an impact on the
strategies and the structure of the pharmaceutical industry and on all aspects of our Health Care
systems.
Applications for marketing authorisations – evolution and opportunities

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1. The Mission statement of the European Medicines Evaluation Agency (EMEA) is to:
   • protect / promote public health
   • pool scientific resources in Member States
   • provide better products and better information
   • promote free movement and the single market
   • provide efficient evaluation of and effective, transparent Marketing Authorisations
   • provide scientific advice for European R&D
   • promote EU harmonisation
   • support international co-operation.

2. As a consequence, there are a number of tasks, which have been laid down to allow the Agency to meet objectives. These include:
   • Evaluation of centralised procedure
   • Provision of scientific advice to companies
   • Provision of regulatory advice to companies
   • Arbitration of decentralised procedure
   • Co-ordination of pharmacovigilance activities
   • Co-ordination of Member States’ inspections
     (G.M.P.’s, G.C.P.s, G.L.P.s)

3. The role of the EMEA is to co-ordinate and manage the evaluation of applications. To do this effectively, a Quality Management System has been put in place to harmonise the way in which various activities are undertaken. The development of this system has involved the analysis of processes and procedures and the generation of a number of standard operating procedures to facilitate these activities. The result has been the provision of a very effective review procedure providing opinions within the time period specified in legislation. In addition, to further help the role the Agency has in co-ordination and managing the centralised procedure, standard operating procedures are used to harmonise the way in which procedures are followed and an EMEA memory is being created by the development of a scientific database to capture precedents.

4. In the context of this conference, there are several advantages, which may be taken from our system and experience, not only by large companies but, also, from small and medium sized enterprises (SME’s). These advantages include the availability of scientific advice in each of the areas of quality, safety and efficacy and the provision of regulatory advice. Although these facilities have been used initially and primarily by large pharmaceutical companies, there is evidence that smaller companies are now coming for such advice. These are identifiable areas where small SME’s and, perhaps, universities may wish to explore. They can come to the EMEA at early stages in the development of their products. The door is open– there is no restriction on when they can come should they want to seek advice. [Note: - A copy of the overheads presented is attached.]
Annex 1

INFORMATION AVAILABLE

- A comment from individual EAG and HLEG members on Commission Communication « Towards a European Research Era »

- Extract from the report of the Workshop « New Safe Medicines Faster »

- Work programme of the Cell Factory key action
A Comment from individual EAG and HLEG Members on:

**Commission Communication**

"Towards a European Research Area"

The undersigned, independent expert members of the Commission’s External Advisory Groups and “High Level Expert Groups” in the Quality of Life and Management of Living Resources feel that our professional credentials and combined experience in advising the Commission on Framework Programme V, give us a strong basis for making useful comments on the concept of a European Research Area.

First of all, we welcome the initiative of EU Commissioner Philippe Busquin to discuss how to develop and share the scientific and technological resources of Europe and thus increase its competitiveness.

Secondly, we agree with the Commissioner that

**“If Europe is not at the forefront of knowledge it is in decline.”**

This statement is particularly valid for those innovative high-tech sectors, such as biotech and the pharmaceutical industry that are expected to generate the most value adding jobs and products in the future.

The communication “Towards a European Research Area” contains many interesting considerations and valuable ideas that reflect a genuine interest in the future of European research and could well improve the conditions for and exploitation of science in Europe if distilled into concrete initiatives.

**General Comments**

We support the Commission’s proposal to reduce the fragmentation of European research activities and to make more efficient use of financial and intellectual resources. The co-operation of the Member States is imperative for progress in this regard. Europe can no longer afford to disperse its human and financial resources in parallel activities in different national institutions. Greater emphasis must be placed on innovation and entrepreneurship at all levels of science and education. However, there is a growing need to support basic sciences and fundamental technologies as well as the associated graduate training. At the time of implementation of Framework Programme VI this need will probably have reached a critical level. Therefore, considerations on how to strengthen basic research in Europe should be initiated now if Europe shall not loose further ground to the US in the field of those groundbreaking sciences and pioneering technologies that are the best basis for true innovation and top-class education.

At the same time as coordination is fostered, it should be noted that, in order to bridge the gap with USA and Japan in basic sciences and fundamental technologies both the Eur. Com. and the member states need to devote more resources for R&D; indeed, with the recent USA and Japanese budgets, the gap indicated (Figure 1, Annex II) in the Commission's proposal is increasing.

The most dynamic areas with high research and development intensity, i.e. the life sciences and information technologies, need optimal support. Furthermore, strong efforts should be made to encourage the interface of technologies between these. Thus, the concurrence of information technology with biotechnology and pharmaceutical research as well as with health care in general will be a key factor for success (e.g. in-silico drug development, virtual research communities, integrated knowledge management, data mining etc.).

In the pharmaceutical sciences and particularly concerning the application of biotechnology, the science-based nature of knowledge is generating networks in which a complex set of relationships has linked large pharmaceutical firms with universities, research laboratories, hospitals, regulatory agencies and biotech companies. The complexity of knowledge, rapid changes in technologies and multiple sources of innovative advancements call for expanding these networks and form new partnerships crossing the boundaries between public and private sectors. Therefore, this process should be expedited through administrative, legislative and financial measures.
Thus, it is particularly important that civil servants in regulatory agencies and administrative bodies as well as legislators are well informed about emerging innovative technologies that may help to develop new and better products. New or improved technologies may also increase the reliability or sensitivity of quality controls. In such cases it is of major importance to the competitiveness of European biotech and pharmaceutical industries that these new procedures are introduced quickly and that requirements for those previous testing protocols that become redundant are removed without unnecessary delay. Since this is in the common interest of the regulatory agencies and the companies, a constructive dialogue between these parties in the European research area should be encouraged.

The limited public understanding of science combined with powerful media messages that reach a wide public immediately and often exert a pervasive effect explains the present trend of opposition to progress in science and technology, in particular to biotechnology. This represents a serious threat to European research as without public acceptance it will be impossible to market the fruits of research and even research in controversial areas will become difficult.

Therefore, concerted efforts should be made to

- Promote a positive image of science by continually emphasising its benefits (new medicines, better food, job creation...).
- Ensure that sound information on scientific breakthroughs, new products and services always are readily available to the public via an official channel with established scientific credibility.
- Continue and stimulate an open debate on controversial new products or processes well before they reach the market using a platform of informed and dedicated individuals from various societal groups (academia, industry, consumers, patients, journalists, politicians) that can provide a credible reference point for science and technology and improve the public perception of science by a correct vulgarisation of the scientific knowledge and the positions taken by platform discussions.

**Specific Comments**

# Grand schemes for mapping, analysing, networking and coordinating are only justified if the considerable efforts made by the contributors are rewarded with significant decisions and effective action. Generally speaking, bottom-up initiatives works best. Having this in mind, approaches to address the following three themes are important:

- Networking of existing centres of excellence in Europe and the creation of virtual centres through the use of new interactive communication tools.
- A common and coordinated approach to the needs and means of financing large research facilities in Europe.
- More coherent and better co-ordinated implementation of national and European research activities.

# The intention of FP5 is to improve the exploitation of European research: “Good Science is not enough, transfer of knowledge is essential”. Although innovation is hard to steer, signs so far are encouraging. As a consequence of this new emphasis, however, support of basic science as well as for talents for talents’ sake including high-quality curiosity driven research has dwindled. Since a similar trend is taking place in several member states, it is of major importance that money can flow quickly and abundantly to where the talents and the teams spearheading new scientific concepts or major technological advances are emerging. This may be achieved by reserving a special fund to the support of “European Research Directors”, i.e. young champions whose groups, for a period of 5 years, should receive substantial funding for trans-European research regardless of the topic as long as it had groundbreaking potential; this necessitates a yearly scientific audit and a decision to prolong funding should be given on a one-year’s advance notice. This scheme may also be used to ensure attractive positions to Europeans working abroad; a special fund could be reserved for female scientists.

# A mechanism should be established to allow consortia (of Member States and/or organisations and institutions) to take the full responsibility for management of selected scientific, technological or educational subprograms or technology platforms for all Europe.
# A major effort should be done to encourage consortia of universities to establish Graduate Schools of Research and/or Research Networks of Excellence at the highest possible international level.

# To ensure the broadest possible country coverage, thus levelling out geographical differences in Europe, EU should match national financial efforts from countries where current R&D expenditures are below the European averages to reinforce their centers of excellence.

# It is important that regional collaborations are encouraged and stimulated. This also applies to “Biovalleys” or other clusters of intellectual, technological and innovative resources. Furthermore, a major effort should be made to nourish the intellectual resources in Eastern Europe that have not had sufficient resources and infrastructure to flourish.

# Regional partnerships are European resources that have not yet been fully exploited. Funds from the Commission as well as national funds could be quickly and well spent on supporting such emerging clusters of science and innovation. Facilitation of bi-national co-operations could be achieved by reserving special funds to double up cash contributions made by two or more European research councils for projects engaging two or more European countries.

# Facilitation of bi-national co-operations could, in a similarly simple way, be achieved by reserving special funds to double up cash contributions made by two or more European research councils for projects engaging two or more European countries.

# The Commission and the Member States should ensure a more dynamic, strong and coordinated European approach towards international issues or cooperation in international fora such as Global Science Forum (previously Megascience Forum) in order to ensure a major impact and sometimes leadership in scientific or technological endeavours (eg. the Global Biodiversity Information Facility or Structural Genomics).

# Major efforts should be done to increase the mobility of European researchers and attract excellent foreign and European researchers working abroad to Europe.

# There are huge opportunities in establishing long-term partnerships with major developing countries such as China, India or Brazil on science, technology, innovation, natural resources and training. Europe should take a much more forceful attitude and be prepared to transfer significant funds to fuel these partnerships.

# Selected major research efforts (eg. new key actions) should strive to involve partners directly representing the interests of the society as for instance clinicians, patients, consumers, and regulatory bodies. A concerted effort to strengthen the pharmaceutical sciences in order to develop new, safe and better medicines faster should encourage establishment of consortia and/or advisory boards including the health care sector, the pharmaceutical industry and medical agencies. The use of biotechnology in clinical practice should be facilitated and involve physicians and patient organisations. In a similar way, programmes to develop transgenic plants and genetically modified food, could be adapted to the real needs as perceived by environmentalists, organic farmers and consumer organisations.

# The biggest challenges facing life scientists today, is how to deal with the huge amount of information available and being produced every day. Since these skills will be crucial for success or failure in the future, all aspects of data management must therefore play a major role in future research and training programmes supported by the Commission including strengthening selected centers of information storage and handling like for instance the European Bioinformatics Institute. “If Europe is not at the forefront of data handling, it is in decline.” A particular challenge is how to bridge the gap between simple systematic data (eg. sequence information) and complex biological data (gene expression patterns, metabolite patterns, images of cells and tissue, spatial reconfigurations in real-time). Bring biology, bioinformatics, and information technology together and science and innovation will flourish.

# In the clinical field, there is tremendous need to build competencies in advanced data-collection and data handling including the use of microsystems, advanced medical equipment and communication technologies.
# While it may be complicated by the fact that this matter involves several of the Commission’s services it is also very important that there should be more consistency between the areas for research funding and health monitoring.

# It has been hard to convince industry to contribute with cool cash to European research consortia. One obstacle has been the complexity and delay in preparing and deciding on applications for the EU programmes. A simple system could rectify this situation: A special fund is reserved to double up the collective cash contributions from one or more public research institutions and one or more companies provided that the project fulfils certain quality criteria and possibly also obligations to undertake graduate training. In return for direct investment in this endeavour the contributing companies must have a first-right-of-refusal on inventions made by the consortia.

# To bridge the gap between idea and application, the Commission should consider to establish or outsource up-scaling or testing facilities that should be available, on easy terms, to upstart companies. Thus, the lack of easy access to GMP facilities for pilot production of biopharmaceuticals is a severe bottleneck in testing and commercialising new potential medicines discovered by small biotech companies in Europe or make GMP approved material available for research purposes at public research institutions. Initiatives to improve this could be modelled on the structure of “Large scale Facilities” (cfr. CERN) or by soliciting (against retribution) time slots in existing (even privately owned) facilities.

# It is of paramount importance for the successful outcome of the European Union’s effort to stimulate science, technology and innovation that the public has had plenty of opportunity to discuss the implications for society.

# It must be ensured that there always are quick and flexible ways of encouraging and supporting individuals or new networks that may bring Europe in the forefront of science and technology. Europe must not miss important opportunities or outstanding talents because of being inflexible or too slow. To be at the forefront of knowledge and innovation, Europe needs speed as well as excellence.

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New Safe Medicines Faster

Proposals for research topics, methodologies, techniques and other means of promoting the drug development process to the benefit of European citizens.

Report from workshop held at Le Plaza, Brussels, March 15-16, 2000

European Federation for Pharmaceutical Sciences - EUFEPS
European Federation of Pharmaceutical Industries and Associations - EFPIA
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The full text of the Report “New Safe Medicines Faster” is available at the EUFEPS secretariat, P.O. Box 1136, SE-111 81 Stockholm, Sweden; e-mail hans.linden@eufeps.org; fax +46 8 4113217, telephone +46 8 7235086
1. Executive summary

A targeted effort to speed up the development of safe, new medicines is sorely needed in Europe. Stronger links between industry, academia and regulatory authorities, more efficient use of modern technology, new methods of drug exploration and targeted training are all vital elements of a streamlining process that cries out to be set in motion. Without it, the European pharmaceutical industry is in imminent danger of losing important ground on global markets – a situation detrimental both to European economies and the patients seeking relief from illness and disease.

Despite being the fifth strongest industry in Europe, the pharmaceutical industry is severely hampered by an approach to drug development and approval that is ill-equipped to exploit the huge opportunities presented by modern drug discovery. Growing demands regarding safety, efficacy and quality documentation consume vast amounts of research and development expenditure. But, at the same time, the average number of years spent on getting a new drug through development and onto the market appears to be on the increase, returning to around 12 years after a brief drop to 10 just a few years ago.

In 1999, the European Federation for Pharmaceutical Sciences (EUFEPS), European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Danish Medicines Agency took the initiative to get the ball of change rolling. A key action entitled “New safe medicines faster” was proposed for the EU’s forthcoming 6th RTD framework programme.

The key action has three main objectives:

- to seek new technology capable of more effective selection of potential drug candidates for innovative medicines while accommodating safety demands
- to use such technology to increase the capacity of and speed up the pharmaceutical development process and eliminate bottlenecks
- to cultivate a pan-European interdisciplinary network that bridges the gap between industry, academia and regulatory authorities

From March 15 to 16, 2000, this proposal was followed up by an EU-supported workshop to identify bottlenecks and speed limitations in the post-discovery phases of drug development and map out a strategy to reduce them. More than 100 representatives from the pharmaceutical industry, academic institutions and regulatory authorities participated in the workshop, producing a description of the research and technology required to bring safe new medicines more rapidly onto the market.

Among the main views expressed was the need for a holistic approach to drug development and research, pulling together all disciplines and specialists from industry and academia and encouraging an earlier involvement by regulatory authorities to alleviate the lengthy procedures involved in drug approval. Attention was also drawn to the lack of new predictive methods which would allow more efficient decision-making and earlier clinical trials. Workshop participants further recommended that centres of expertise be established to provide scientists with multidisciplinary training in modern technology.

The diversity of the entire drug development process is too great to be covered by a single workshop. But, as the results obtained from the workshop’s seven sessions suggest, an EU-supported effort by industry, academia and regulatory authorities may be the most appropriate means of setting new European standards – bringing new medicines onto the market faster and in a more cost-effective way and establishing Europe’s pharmaceutical industry as the best and most competitive in the world.
Quality of Life and Management of Living Resources
Extract from the Workprogramme 2000

KEY ACTION 3: THE “CELL FACTORY”

Objectives and Deliverables

The integration of innovative research and technologies with their exploitation by industry and/or other socio-economic entities in the fields of health, environment, agro-industry, agri-food and high value added chemicals is the aim of this key action. Particular attention will be given to the problem solving approach of strengthening European industrial competitiveness by improving the potential for creation of small research-based biotechnology firms and entrepreneurial initiatives. These knowledge-based new industries are a reservoir of industrial competitiveness, scientific and technological innovation, opportunities for investors, and jobs creation, which is still underexploited in Europe.

An environment in which scientific results could be rapidly exploited and transformed into products and processes of interest to society will be provided, through integrating the whole process of innovation, from advanced research, through technological development up to demonstration. Such an integrated innovation approach is an absolute pre-requisite in this key action, but the exploitation phase may also be a non-industrial one, depending on the particular socio-economic environment associated with a given scientific and technological area, e.g. biosafety research to be used by public-interest organisations, in-vitro alternative testing to replace animal experimentation, research results to be used by clinicians and in hospitals.

This key action will therefore mobilise the necessary operators (e.g. scientists, industrialists, venture capitalists, “biovalleys” and “bioincubators” for nurturing start-ups, consumer and patient’s associations, public-interest groups) to address the following objectives in a co-ordinated and convergent way, linking the ability to discover and the ability to exploit:

- Innovative technologies mobilising mission oriented research. New knowledge will be generated on the functioning of cells, including GMOs, as biological factories, by advanced research such as genomics, proteomics, patterns of metabolites, combinatorial biochemistry, high-throughput screening, nanobiotechnology, structural biology, molecular evolution, bioinformatics, genetic and biochemical engineering. These multidisciplinary technologies applicable to many fields of the cell factories will provide new processes and molecules, for implementing the priorities given in the workprogramme.

- Exploitation of RTD results. Scientific and technological excellence is necessary but not sufficient. It must be closely linked to a firm commitment to knowledge transfer and to convincing exploitation by industry and/or public interest organisations. Efficient risk capital markets, creation and development of high-tech SMEs, and promoting the dialogue of technology producers with technology users are crucial for linking research to socio-economic needs, leading to future wealth and job creation. The challenge is therefore to set up a nurturing environment both for the development of established bio-industries and for a new generation of European entrepreneurs to start up and flourish.

Towards the anticipated deliverables: improving the competitiveness of established bio-industries and triggering the creation and sustaining the growth rate of new biotech research-based industries, European players should be mobilised to seize opportunities in the following 3 priority areas:

- Improving the diagnostic and therapeutic arsenal for health care.

  Anticipated deliverables: New and improved health related processes and products from living cells and biomolecules, in particular towards diagnostics tests, innovative technologies for biological production, novel targets for drug discovery, novel and improved therapeutics for health care (such as new antibiotics, anticancer therapies...) and development of in-vitro tests as alternatives to animal experimentation.
- Improving environmental sustainability.  

- New biological and biotechnological products and processes for agro-industry, agri-food and high value added chemicals 
  Anticipated deliverables: Bio-processes and products offering ecological, industrial and consumer advantages, high value-added products and processes for agro-industry and (bio)chemical sectors, biocatalysts, nanobiotechnology devices, and products derived from improved organisms, including GMOs.

**Priorities for the 2000 calls**

Projects must combine excellent science and convincing exploitation strategies

According to the objectives and problem solving approach of this key action, all projects to be supported must mobilise scientific excellence, innovative technologies and convincing exploitation strategies by bio-industries, entrepreneurial initiatives, hospitals and/or public-interest groups as appropriate, and taking into account the socio-economic context, including the intellectual property rights. The projects must fulfil this absolute pre-requisite. Depending on their goals, the applicants are also invited to consider either the specific mission-oriented approaches of other key actions or the building up of a new knowledge base in the generic activities. Provided the projects do satisfy the above pre-requisite, they may address a wide spectrum of targets. Consequently, and in order to leave room for innovative ideas from applicants, each of the following RTD priorities only give “aspects for consideration” which are non-exhaustive examples.

**3.1. Improving the diagnostic and therapeutic arsenal for health care**

3.1.1. Development of new diagnostics

Aspects for consideration: new diagnostic tests and procedures aimed at detecting early markers and weak signals in pathology, including near-patient diagnostic tests, tests to ensure the safety of biological fluids, nucleic acid diagnostic tests, and *in-vivo* imaging. Quality control and safety aspects of diagnostic tests will also be addressed.

3.1.2. Therapeutic substances

Aspects for consideration: design and development of new therapeutic substances such as antibodies, antimicrobials, anticancer, and other bio-active compounds to be used in therapy. Improved, safe and efficient production of therapeutic substances, including vaccines, by micro-organisms, plants or animals. Innovative screening of new therapeutic substances, including those based on analysis of complex genetic and physiological data.

3.1.3. Therapeutic strategies

Aspects for consideration: Development of nucleic acid and cell therapies, cell and tissue engineering and target specific delivery systems. Development of cell lines for cell mediated gene therapy and of biological substitutes that restore, maintain or improve tissue and organ functions.

3.1.4. Novel *in-vitro* testing as alternatives to animal testing

Aspects for consideration: reinforcement of pre-normative research by making cell cultures available as a substitute for animal testing, development of high throughput screening for detecting toxicity, and *in-vitro* toxicity tests, e.g. local toxicity, immuno-toxicity, neuro-toxicology.
Annex 2

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