DRAFT

The Innovative Medicines Initiative (IMI)
Strategic Research Agenda

Creating biomedical R&D leadership for Europe to benefit patients and society

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Executive Summary

One of the major objectives of the European Union (EU) is to build the most competitive and dynamic knowledge-based economy in the world by 2010[1]. A key element of this objective is the strengthening of the science base in Europe. The biopharmaceutical environment is characterized by its focus on science and innovation. It is therefore essential to revitalize the biopharmaceutical research and development (R&D) environment for Europe to become more competitive. Furthermore, strengthening the biomedical R&D environment will benefit patients and society by increasing the efficacy of drug discovery and development.

The Innovative Medicines Initiative proposes clear practical paths to accelerate the development of safe and more effective medicines by joint public and private collaborations.

This document sets out the Strategic Research Agenda for the Innovative Medicines Initiative. Bottlenecks in the biomedical R&D process have been identified and recommendations on how to address these bottlenecks have been developed using a pre-competitive approach. The specific recommendations presented in this document are outcomes from consultation of the relevant stakeholders during 2004 and 2005.

The recommendations are organised around four main topics: improved predictivity of safety evaluation, improved predictivity of efficacy evaluation, improved knowledge management and improved education and training to develop the talent base needed for the EU biomedical environment of the future.

Safety:

The main recommendations concerning safety evaluation are:

- Create a European Centre of Drug Safety to identify and co-ordinate research needs in safety sciences,
- Establish a framework to develop biomarkers that will indicate the human relevance and regulatory utility of early laboratory findings,
- Develop in silico methods for predicting conventional and recently recognised types of toxicity.

Efficacy:

The main recommendations concerning efficacy evaluation are:

- Stimulate translational medicine in an integrated fashion across industry and academia,
- Create disease-specific European Imaging Networks for establishment of standards, validation of imaging biomarkers and development of regional centres of excellence,
- Develop a partnership with regulators to devise innovative clinical trial designs and analyses, to aid acceptance of biomarkers and to promote data sharing and joint consideration of ethical issues.

Knowledge Management:

In the biopharmaceutical R&D process an enormous amount of data is created. A critical factor is the ability to turn this mass of information into actionable knowledge. This has been addressed in the Knowledge Management working group, the main recommendations are:

- Develop enhanced knowledge representation models and data exchange standards for complex systems,
- Build a core reference database of validated experimental data extracted from the literature,
- Design standards for and build an expert tool to allow the federation of local databases in a secured environment.

[1] See Chapter 1, page 9 for references on the European Union objectives.

Education and Training:

The main recommendations concerning Education and Training (E&T) are:

- Create a European Medicines Research Academy for education and training for professionals involved in biomedical R&D including regulatory officers over the whole lifecycle of a medicine,
- Map existing activities within E&T including identification of European centres of excellence and develop programmes and implementation plans for the critical areas relevant to the biomedical R&D process,
- Evaluate options to foster mobility between academia and industry.

Each year for a period of 7 years, 440 million euros will be required to implement these recommendations (see page 101 for a breakdown). It is foreseen that the European Commission together with the biopharmaceutical industry will contribute equally to the funding of these research projects through the creation of a separate legal structure.

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Abbreviations Used

AD	Alzheimer's Disease
ADRs	Adverse Drug Reactions
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
DB	Database
EBE	Emerging Biotechnology Enterprises
EC	European Commission
ECTP	European Centre of Toxicologic Pathology
EFB	European Federation of Biotechnology
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMEA	European Medicines Agency
EPF	European Patients Forum
ETP	European Technology Platform
EU	European Union
EUFEPS	European Federation for Pharmaceutical Sciences
FP	Framework Programme
GDP	Gross Domestic Product
GLP	Good Laboratory Practices
IMI	Innovative Medicines Initiative
IP	Integrated Project
IPRs	Intellectual Property Rights
IT	Information Technology
KM	Knowledge Management
NCE	New Chemical Entity
R&D	Research and Development
RDG	Research Directors Group
SME	Small Medium Enterprise
STRPC	Science Technology Regulatory Policy Committee
SRA	Strategic Research Agenda

1 Introduction

Europe has lost its leading place as a global centre for biomedical research. Despite a five-fold increase in the Pharmaceutical trade surplus over the last 10 years, investment in research and development (R&D) is declining markedly in comparison with the US (Figure 1). Over the past ten years, Europe's research and development basis has gradually eroded, with new leading-edge technology research units being transferred out of Europe, mainly to the United States. Whereas R&D investments in Europe grew by 2.6 times between 1990 and 2003, the corresponding increase in the U.S. is more than fourfold. In 1990, major European research-based companies spent 73% of their worldwide R&D expenditure on the EU territory. In 1999, they spent only 59% on the EU territory. The USA was the main beneficiary of this transfer of R&D Expenditure.

In 2004, the pharmaceutical industry invested about 21.5 billion euros in R&D in Europe. This amount consists of:

- 6.9 billions euros for discovery and pre-clinical development,
- 1.5 billions euros for phase I clinical trials,
- 2.4 billions euros for phase II clinical trials and,
- 10.7 billions euros for phase III clinical trials, regulatory approval and Pharmacovigilance.

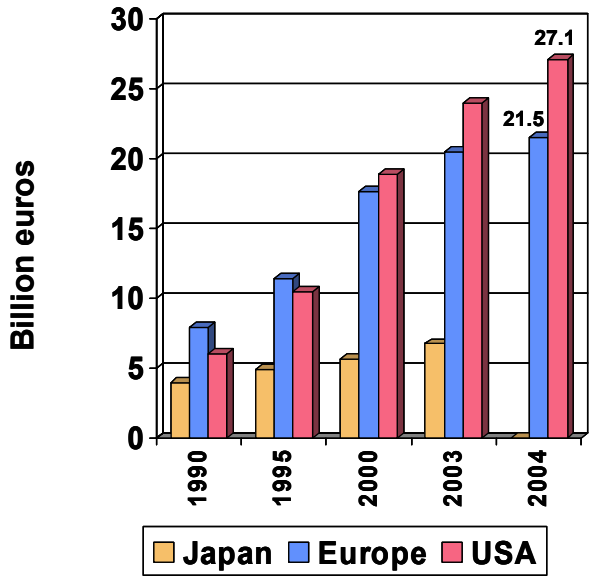

Figure 1: Pharmaceutical R&D expenditure in Europe, USA and Japan 1990-2004[2]

Over the last decade, the US has invested far more in public sector sponsored biomedical research, and Europe has not yet matched this level of public sector investment (Figure 2). Thus, between 1998 and 2003, the US government doubled the funding for the National Institutes for Health. This is affecting, and will continue to affect growth and development in Europe to the detriment of both patients and society. Direct health R&D funding actually fell in the late 1990s in a number of countries.

[2] EFPIA member associations, PhRMA, JPMA, Data 2004: estimate EFPIA & PhRMA (billion euros at 2003 exchange rates)

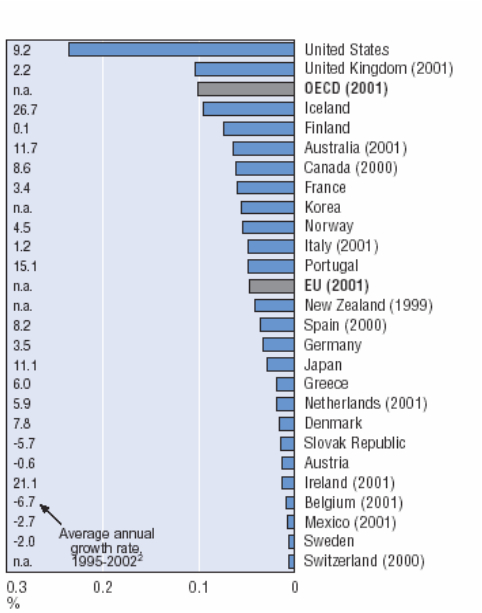

Figure 2: Health R&D in government budgets as a percentage of GDP, 2002[3]

The Innovative Medicines Initiative addresses the complex issues associated with the future of biomedical research within the EU, and addresses ways of achieving accelerated development of new, safe and more effective medicines that will help revitalize the European biopharmaceutical research environment.

The discovery and development of new drugs is very resource intensive, and the rate of failure of drug candidates is high. Initiatives to reduce the rate of attrition during later phases are clearly desirable and if successfully implemented will increase the efficacy of drug development, then Europe can again become a place where industry chooses to invest. EFPIA's Research Directors Group has identified pre-competitive barriers to innovation, around which industry and stakeholders in the drug R&D process can collaborate to achieve this goal. The barriers on which this proposal is focused are the failure of preclinical studies to predict safety and efficacy in the clinic, along with the regulatory process, which needs to keep pace with scientific developments. Improvements in predictive biology and the incorporation of these new concepts into an improved regulatory framework would decrease the cost of drug development and speed up the delivery of innovative medicines to patients.

The objectives of the Innovative Medicines Initiative are ambitious but within the reach of an industry that realises the need to address these issues. Once the project is completed the results will not only help speed up the process for drug development but will also revolutionise and completely change the process by which drugs are developed.

Research carried out in the Integrated Project InnoMed, supported by the European Commission under the third call of the 6th Framework Programme, which deals with predictive toxicology and with discovery and validation of new markers for diagnostics, disease progression and therapeutic efficacy in Alzheimer Diseases illustrates the value and role of these types of approaches.

1.1 European Technology Platform

On January 23, 2002, the European Commission published its Communication on Life Sciences and Biotechnology – a Strategy for Europe[4]. These areas, life sciences and biotechnology, are widely regarded as one of the most promising frontier science and technology areas for the coming decades. Life sciences and biotechnology entail and foster the development of many enabling technologies – like information and nano-technologies – and cover a wide range of applications with benefits in both the public and private sectors. On the basis of scientific and technological breakthroughs in recent years, the explosion of genomic

[3] OECD, R&D database, June 2003

[4] http://europa.eu.int/comm/biotechnology/pdf/com2002-27_en.pdf

data on living organisms is posed to spur much new research and applications in the future according to the Commission communication.

The High Level Group on innovation and provision of medicines, which brought together different stakeholders (European Commission, government representatives, industry, patients and healthcare providers) agreed on the following recommendations relating to the research and development environment (Recommendations 8 and 9 of the G10 report 'Stimulating Innovation and Improving the EU Science Base'[5]).

- *Recommendation 8*: The creation of the European virtual institutes of health, connecting all existing competence centres on fundamental and clinical research into a European network of excellence.
- *Recommendation 9*: To improve the co-ordination of Community and national activities, by:
  - Commission and Member States to co-ordinate and support the conduct of clinical trials on a European scale, establish a database of trials and clinical research results,
  - Commission and Member States to put in place an effective policy in terms of incentives to research and support the development and marketing of orphan and paediatric medicines,
  - Supporting the development of a biotechnology strategy in Europe.

In March 2000 in Lisbon, the European Council agreed on the Lisbon objectives, stating, "the Union must become the most competitive and dynamic knowledge-based economy in the world capable of sustainable economic growth with more and better jobs and greater social cohesion". The ambitious goal was to achieve this by 2010, by having Europe invest 3% of its GDP in R&D; this was envisaged being achieved via one third from the public sector and two thirds from the private sector. To support the Lisbon objective, a communication from the Commission from June 2004[6], acknowledged the need to double the Union's research budget and emphasised the launch of European technology initiatives. In the same paper, the need for a European level co-ordination of research efforts and for the development of research infrastructures are presented as key factors to stimulate research in Europe.

In this context the European Commission developed the European Technology Platform (ETP), a concept developed to identify and propose ways of addressing major economic, technological or societal challenges enabled by Research and Development. It is intended as a means to foster effective public-private partnerships between all relevant stakeholders, in effect to establish and implement Strategic Research Agendas. Technology Platforms bring together companies, research institutions, the financial world and the regulatory authorities at the European level to define a common research agenda which should mobilise a critical mass of - national and European - public and private resources. Technology Platforms are expected to contribute to achieving the Lisbon objectives, developing the European Research Area and increasing investment in R&D towards the 3% of GDP target. This intention was published in the Communication from the Commission entitled "Science and technology, the key to Europe's future – Guidelines for future European Union policy to support research"[7].

Based on this the European Commission asked EFPIA's Research Directors Group (RDG) to identify main barriers to innovation in Life Sciences research in Europe with the objective of establishing a European Technology Platform for Innovative Medicines. The RDG has already identified main pre-competitive barriers to innovation, around which industry and stakeholders in the drug development process can collaborate to achieve a first class environment for R&D. This document is intended to present the Strategic Research Agenda developed by all relevant stakeholders during the last 10 months.

There are many possibilities and opportunities that will help Europe towards more efficient drug development, examples include:

- Leverage expertise in new technologies for identification and validation of biomarkers,
- Manage and organise data to create knowledge to predict benefit and risk of new therapies for all stakeholders in the drug development process,

[5] http://pharmacos.eudra.org/F3/g10/g10home.htm

[6] Science and technology, the key to Europe's future – Guidelines for future European Union policy to support research

[7] COM(2004) 353 final

- Improve dialogue with regulators during development prior to regulatory approval to help reduce requests for additional data and regulatory questions following submission,
- Build and support pre-competitive research centres and a European network of centres of excellence.

Initiatives such as these must be funded, co-ordinated and targeted to have the maximum impact, and this is where the creation of a Joint Technology Initiative (JTI) to manage the projects, as proposed by the European Commission, is both important and relevant.

To be effective, the Joint Technology Initiative must deliver added value to the drug discovery and development process, and to individual stakeholders. The collective benefit is expected to come from a transparent, total-systems approach to the discovery and development process. This enables each player to appreciate more fully the roles and needs of the others, and to be able to make non-traditional contributions in areas beyond their own.

1.2 Bottlenecks in the biomedical R&D process

The development of a new drug is long, resource intensive and complex. The overall cost is variously estimated at between $400 and $900 million (US) for the period 1994-2000[8]. The possibility of failure to reach the market is high and the project may fail for many reasons at many points in its evolution. Data on product attrition rates indicate that the probability of a drug candidate passing from pre-clinical stages (first GLP toxicity study) to market is 6% or less[9]. Reducing the risk depends upon a concerted research effort to address the perceived bottlenecks in the development pathway. The greatest need for the pharmaceutical industry is to detect the possibility of failure at the earliest stage as possible, and it is in this context that advances in basic biomedical science within the European research community could make the greatest contribution. The reasons for failure to develop drugs to the stage of marketing are shown below.

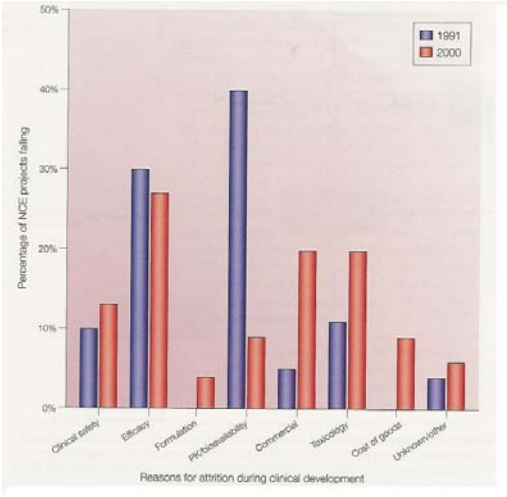

Figure 3: Reasons for attrition[10]

The commonest factors resulting in project failure are either lack of efficacy (25%), clinical safety concerns (12%) and toxicological findings in pre-clinical evaluation (20%). The biggest advance between 1991 and 2000 has been in improving the predictive value of studies of drug metabolism in optimising drug design. This has been possible because in-vitro screens of absorption and metabolism have been validated by subsequent correlation with clinical measurements. The Innovative Medicines Initiative with an academic, industry multi-disciplinary collaboration aims to achieve similar clinical correlations within the other areas

[8] DiMasi JA Hansen RW Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of Health Economics 2003 Mar;22(2):151-85

[9] Industry Success Rates 2004, Centre for Medicines Research International Ltd. CMR04-234R, May 2004

[10] A survey of pharmaceutical companies comparing reasons for attrition, between 1991 and 2000, expressed as a percentage of all drug projects stopped during clinical development Nature Rev. Drug Discov. 3, 711-715, (2004)

mentioned in figure 3. These improvements can be related to the different stages of drug discovery and development.

The objective for the future would be to identify as soon as possible a lack of efficacy, despite promising pre-clinical data and the potential for adverse drug reactions and pre-clinical toxicity.

The identified key bottlenecks in the R&D process are shown in the figure below. In these areas, scientific and technological advances, as would be gained with the ETP would be of direct benefit to medicine development by improving efficiency. In addition, a more efficient R&D process will bring more efficacious and safer drugs to the market more quickly, resulting in a direct benefit for patients. The Strategic Research Agenda addresses issues in all of these areas, and proposes specific areas of research in these topics to improve the overall efficiency of medicine development.

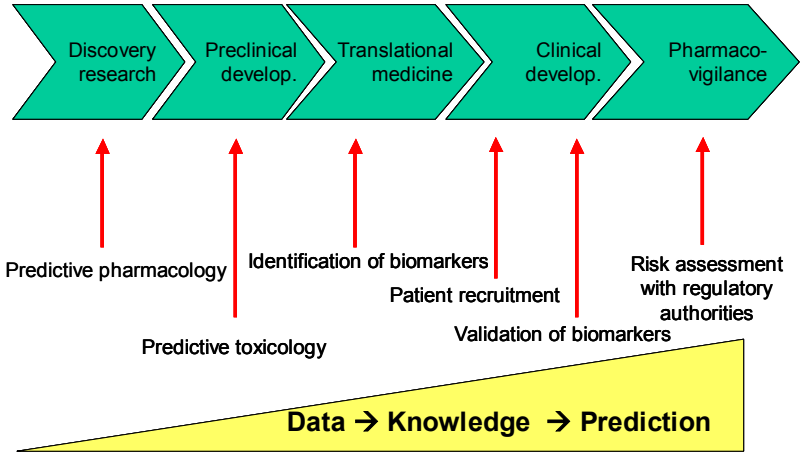

Figure 4: The pharmaceutical R&D process and key bottlenecks

1.3 Strategic Research Agenda

The proposed Strategic Research Agenda (SRA) encompasses the whole path from discovery of a new drug target to the validation and approval stages of a new drug compound. The SRA addresses key areas, which are linked to the bottlenecks in current drug development and also includes regulatory aspects.

Over the last years, therapeutic discoveries and innovation have leapt forward placing the patient at the centre of the research process and because of this there is an opportunity to advance knowledge about the mechanisms underlying pathologies and drug activities. To accelerate the development of more effective medicines, safety and efficacy evaluation of new molecular entities needs to be improved. The proposed Strategic Research Agenda will be organised around four key areas, addressing the key bottlenecks in the R&D process (Figure 4). They are:

- Safety, addressing the bottlenecks of predictivity in safety evaluation and pharmacovigilance with the authorities
- Efficacy, addressing the bottlenecks of predictive pharmacology, biomarkers identification and validation, patient recruitment and risk assessment with the authorities
- Knowledge Management, leveraging the potential of new technologies to analyse a huge amount of information in an integrated and predictive way
- Education and Training, addressing certain gaps in expertise which need to be resolved in order to change and support the biopharmaceutical research and development process

The knowledge management area will be key to leveraging the potential of new technologies such as genomics and proteomics and to analyse the huge amount of information in an integrated way. The education and training work package will identify and address specific gaps in expertise, which must be resolved in order to support the needed changes identified in the SRA. The education and training work package will also ensure that the utmost is done to achieve excellence in the European biomedical education landscape.

The long-term benefits to this approach will be to:

- Get medicines to patients more quickly,

- Discover and develop better medicines, which will be safer, have improved efficacy and will be better adapted to patients needs,
- Facilitate risk / benefit evaluation by the authorities to accelerate access of innovative medicine to patients.

The SRA involved relevant stakeholders to define precise recommendations in four key areas that need to be dealt with collaboratively in the lifecycle of drug development.

The main ambition of the Innovative Medicines Initiative is to co-ordinate investments in these areas across the drug development process to achieve critical mass and synergies that will benefit all stakeholders in Europe. The interaction between these four cornerstones of the SRA is shown below.

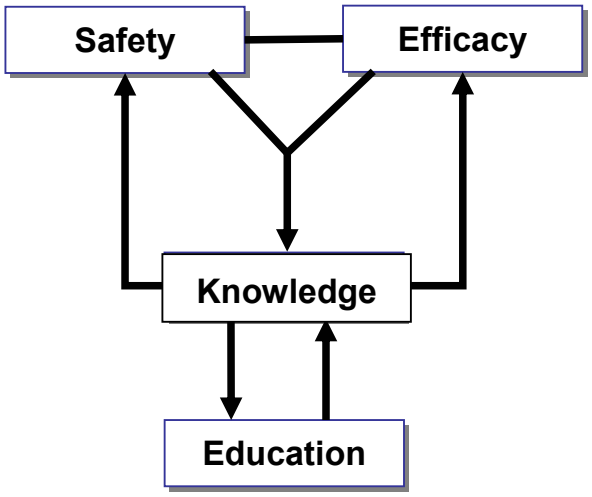

Figure 5: Strategic Research Agenda interactions

Safety

Regulatory authorities, reflecting and sometimes leading society, are becoming more risk-averse, requiring ever broader and more restrictive risk management strategies to avoid real and perceived risks. The result has been requirements for expanded studies to quantify potential serious adverse events, even ones of great rarity or scientific improbability. The reasons for this may include increased public and media scrutiny of pharmaceuticals and regulatory decision-making, and a perceived lack of robustness of the post-marketing monitoring processes. In addition, there is an increasing tendency for approval of more restricted indications (with requests for increased data for broader indications); this can lead to significant delays in gaining marketing authorisation and delay patient access to innovative medicines that address medical needs. The following suggestions are intended to enhance this overall process.

The SRA addresses safety concerns by:

- Establishing processes to improve the predictability of safety testing using integration of new technologies such as toxicogenomics, toxicoproteomics, toxicometabonomics and enhances in silico predictive techniques,
- Involving the regulatory authorities in the development of these new processes so that the data can support the risk/benefit evaluation process,
- Research carried out in the Integrated Project InnoMed that deals with ‘omics technology applications in toxicology and mechanistic investigations,
- Introducing measures to improve healthcare provider training, development of databases including knowledge management tools of data analysis and measures to improve communication between patients, physicians and other healthcare providers on the risk and benefits of medicines.

Efficacy

Along with improved early safety evaluation there is another strategic requirement if the availability of improved medicines for society is to be enhanced. This is an improvement in clinical research including translational medicine.

Within the Innovative Medicines Initiative, the improvement in clinical research with regards to efficacy and patient recruitment will be addressed within the following actions:

- Better understanding of disease mechanisms,
- Improve prediction of efficacy using biomarkers,
- Develop strategies towards enabling development of medicines which will be better adapted to patients' needs,
- Improve patient selection using biomarkers and enhance recruitment through consultation with patients and clinical groups,
- Increase clinical trial capacities and capabilities across Europe,
- Increase the dialogue with regulatory authorities in order to shorten or reduce the cost of clinical development.

Knowledge Management

The goal of this workpackage is to provide input on technology required for establishing a Knowledge Management (KM) environment capable of supporting the scientific objectives of the Strategic Research Agenda, to identify gaps in current technologies and to offer recommendations on how to bridge those gaps.

Within the Innovative Medicines Initiative, the scientific requirements are addressed by the following actions:

- Develop a strategy to identify the areas of interest to all stakeholders,
- Provide mechanisms for data federation across heterogeneous data sources,
- Provide a flexible and secure collaborative environment serving all stakeholders,
- Provide standards and mechanisms for consistent data integration and data sharing,
- Provide standards and mechanisms for consistent integration of complex scientific tools and computational models,
- Insure interoperability of computing services across organizations,
- Develop broad and generic research projects for bridging gaps in current technologies.

Education and Training

The Strategic Research Agenda proposes changes to the way contemporary medical R&D is performed. The identified gaps and bottlenecks are addressed by new technologies and new paradigms for assessment of safety and efficacy as well as for medical practice. This also calls for identification and addressing gaps and bottlenecks that exist in the education and training of scientists who will be, or are, involved in the development process.

A number of gaps within education and training have been identified:

- The current organisation of universities facilitates the creation of "silos" where each scientific area has its own life without much interaction with other areas. This is contributing to the fragmentation of European research[11,12],
- There are weak or non-existing links between basic scientists and clinical scientists. This gap is critical and is not yet bridged. Efforts are proposed in the field of translational medicine to bridge

[11] Wilson EO, Consilience : The Unity of Knowledge. ISBN: 0679450777

[12] Busquin P, At the 'Communicating European Research' conference on 11 May 2004 http://ica.cordis.lu/search/index.cfm?fuseaction=news.simpledocument&N_RCN=22027&CFID=994044&CFTOKEN=61399528

this gap from "bench to bedside" – and back again by combining a thorough understanding of the biology of a disease with the clinical picture[13],

- Physicians practising Pharmaceutical Medicine should be provided adequate education and training to maintain a broad-base expertise to enhance the efficiency of these professionals to be instrumental in translational medicine,
- There is a need for safety scientists with a much broader spectrum of knowledge than the traditional toxicologist. The future safety scientist will have to integrate knowledge accumulated from many safety-relevant disciplines (primary and secondary pharmacology, functional genomics, safety pharmacology, physiology, pathophysiology, physical chemistry, animal and clinical toxicology cellular biology; biochemistry and animal physiology with all their special branches) to excel in modern risk assessment and risk management[14],
- In most European countries the scientific interaction between scientists in academia, industry and regulatory authorities are minimal and often the movement of intellect is uni-directional towards the industry. However, scientists from academia and regulatory agencies need to be involved and have access to new technologies,
- European education needs to strive for excellence and competitive systems need to be put in place for a continuous improvement of the scientific level in Europe.

To identify ways to overcome these gaps, consultation with the involved stakeholders has been carried out in order to propose how to reorganise education & training and to design specific training programmes.

Within the Innovative Medicines Initiative this has been addressed with the following actions:

- Consultation with stakeholders to further analyse the gaps within education and training,
- Consultations with stakeholders to discuses creation of a pan-European platform for research, research training and technology development supporting the entire medicines development and approval process,
- Development of a curriculum for the safety scientist,
- Proposal on how to facilitate exchange programs for scientists between academia and industry.

1.4 Stakeholder involvement

The opportunity to address unmet medical needs has never been greater but spiralling costs threaten to make the development of new drugs increasingly unaffordable for both developers and patients alike. Every effort must be made to make the drug development process more efficient, faster and more predictable. To be effective, the problem must be addressed by the active participation of all relevant stakeholders (academia, clinicians, patient organisations, large industry, SMEs, regulatory and ethics specialists). The collective impact is expected to come from the transparent, total-systems approach to the discovery and development process and in so doing enables each player to appreciate more fully the roles and needs of the others.

Figure 6 presents some of the direct benefits of implementing the Strategic Research Agenda for various stakeholder groups along with the expected long-term impact.

[13] Mankoff SP & al, Lost in Translation: Obstacles to Translational Medicine, Journal of Translational Medicine 2004, 2:14

[14] EUFEPS 2004, Report from EUFEPS Brainstorm Workshop on Safety Sciences, Brussels, April 2-3 • 2004

Stakeholders	Benefits	Long term impact
Patients and patient organisations	• Influence on the research agenda for new medicines, • Influence on quality of life measures for new medicines.	• Faster access to more efficacious and safer medicines, • Improved quality of life though improved/more appropriate therapies, • Improved quality of life through increased national GDP/capita.
Clinicians	• A mechanism for influencing the development of more appropriate therapies and adding to their armoury of treatment options.	• Better diagnostic tools and methods.
Governments	• Contribution to the Lisbon agenda	•
Treasuries	• Providing a forum for increased commercialisation of pharmaceutical research.	• Increased GDP/capita through the increased international competitiveness and growth of the European based bio-pharmaceutical industry, • Reduced cost of working days lost to disease, • Positioning Europe as the leader in pharmaceutical and biopharmaceutical R&D, raising its international profile, attracting international partnerships and inward investment, • Creation of jobs / reverse movement of high skill jobs from Europe.
Health Departments	• Improved integration of the development of therapies for unmet medical needs.	• More effective therapies will mean more efficient treatment and reduced costs for long term care.
European Institutions	• Contribution to the Lisbon agenda.	•
Regulatory agencies	• Development of new risk/benefit assessment methods in collaboration with all relevant stakeholders.	• Improved process and productivity through better data sharing.

Stakeholders	Benefits	Long term impact
Industry		
Pharmaceutical industry	• Better leverage of scientific data between companies and between all stakeholders in the R&D process.	• Reduced risk and a more productive drug pipeline.
SMEs	• Risk reduction in entering clinical trials due to access to safety data not earlier available, • Possibility for more partnerships for proof of principle studies, • Partial financing of technology development.	• An improved environment for discovery and early stage development of enabling technologies, diagnostics and potential therapies, • Lower R&D risk should facilitate access to venture capital.
Insurance industry		• Reduced liabilities for long term care.
Other economic sectors		• Reduction in costs and lost production through illness.
Academia		
Researchers	• A framework within which to bid for work in priority areas and to establish collaborations (national and international), • An information source to facilitate definition of competitive and relevant R&D programmes, • A better infrastructure including top-notch technological equipment, • Publication.	• Establishment of a different partnership with industry and other stakeholders.
Research Councils & other funding bodies	• A framework within which to gain an overview of current research programmes, avoid duplication and gain cross disciplinary and cross institutional synergy.	• Input to targeted long term strategic planning for funding programmes.
General public		• Increased awareness of diseases, their symptoms and consequences.
Charities		• Improved quality of life for specific diseases.

Figure 6: Impact on stakeholders

The European Commission organised an initial consultation of stakeholders in Brussels on October 5th and 6th, 2004. That meeting had two main conclusions. Firstly, an important need for more information exchange between the different entities involved in biomedical research was identified as critical. Secondly, the forum agreed with the list of issues to be addressed as proposed by the research directors from the pharmaceutical and biotechnology companies. The report from this meeting can be found on the EC website at ftp://ftp.cordis.lu/pub/lifescihealth/docs/tp_innmed_conclusions_meeting_5-6_oct_final1.pdf.

Subsequently, between January and May 2005, the European Commission and EFPIA organised a series of thematic workshops to develop the Strategic Research Agenda involving all the relevant stakeholders. In addition, in Barcelona on April 21st and 22nd 2005, the overall strategy was presented to participants representing all organisations involved in the discovery and development of new medicines in Europe. The report from this meeting can be found in Appendix 1.

A total of 327 experts of the R&D process have been formally consulted since January 2005, they represented the different sectors of activities in a balanced way as shown in figure 7.

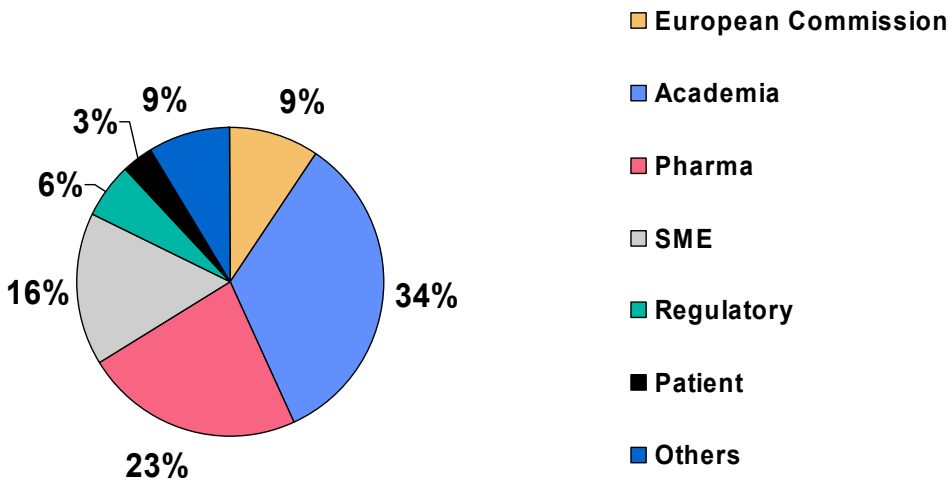

Figure 7: Stakeholder contribution to the Strategic Research Agenda

1.5 Contributions to standards

The Innovative Medicines Initiative will not contribute to international standards *per se* but the different topics addressed by the initiative will evaluate new approaches to drug discovery and development. Its potential to change the biopharmaceuticals research and development process is based on a more systematic use of biomarkers and on leveraging highly innovative technologies such as 'omics technologies and other types of data in combination with appropriate knowledge management models. It is foreseen that the results gained will provide input to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

This European initiative may also contribute to the cooperation between the EMEA and the FDA concerning innovation and R&D regulatory hurdles.

If the use of biomarkers is generalized for preclinical and clinical investigations, the initiative will contribute though intensive discussions within the proposed networks to agree on new approaches and European standards to validate biomarkers and to evaluate risk and benefit for the patient. This approach will also favour cross-functional collaboration between pre-clinical and clinical scientists and promote the development of translational medicine.

In addition, a main focus of the project is to change the way the different stakeholders work together. This will lead to the establishment of a new type of collaboration between industry, academia, clinicians and patients and a real paradigm shift in culture. Ultimately, this will also lead to better and easier interactions with the pertinent Regulatory Authorities.

2 Improved Predictivity of Drug Safety Evaluation

2.1 Summary

This section addresses the problems and bottlenecks currently present in drug safety testing. There is a need to enhance the predictivity of safety to help alleviate the current high attrition rate in drug development in Europe. A project has been proposed to enhance the prediction of toxicity by integrating the new 'omic technologies with conventional toxicity endpoints. This has been submitted under the 6th Framework Programme (FP6). This is anticipated to bring in some increases in predictivity, but major additional gains in predictivity can be made.

Formation of a small European Centre for Drug Safety (ECDS) is proposed to co-ordinate research efforts in this area, enhance training and education of drug safety scientists and to realise the benefits of knowledge management in this area. Specific research projects are described that would be co-ordinated by the proposed centre i.e. a proper framework for biomarker development that will include the FP6 project, determination of the relevance of non-genotoxic carcinogens, development of better and more widely applicable *in silico* models of toxicity and a better understanding of so-called 'intractable toxicities'.

The profiling of the ECDS was initially focusing on non-clinical issues, but subsequent discussion emphasized the urgent necessity to integrate Clinical Safety and Pharmacovigilance into the activities of the ECDS. A detailed analysis on the specific needs and requirements is ongoing and details on priority programmes have to be more extensively profiled in the near future.

The main recommendations concerning Safety Evaluation are:

- Create a European Centre of Drug Safety to identify and co-ordinate research needs in safety sciences,
- Establish a framework to develop biomarkers that will indicate the human relevance and regulatory utility of early laboratory findings,
- Study the relevance of rodent non-genotoxic carcinogens,
- Develop in silico methods for predicting conventional and recently recognised types of toxicity,
- Explore the implications of intractable toxicity in animal for human risk,
- Improve healthcare provider training in detection and reporting of adverse drug reactions,
- Develop knowledge management tools to allow access, search and analysis of existing databases as well as to allow the development and federation of new databases,
- Improve communication between patients, physicians and other healthcare providers on the risks and benefits of medicines.

An outline of the funding needed to set up and run the ECDS and to support the chosen projects is included.

2.2 Introduction

2.2.1 Non-clinical (Pre-clinical) Safety

The current best available methods for making judgments to predict safety use animals alongside non-animal tests. These animal tests predict 70-90% of toxicities[15].

Improved predictivity of early safety evaluation to further cut the rate of attrition will thus bring efficiencies in successful drug development. There should also be a realistic appreciation of what animal based tests can, and cannot provide to Regulators to understand drug safety in humans. There will be animal welfare benefits if non-animal tests can replace or improve predictivity.

[15] Nature Reviews Drug Discovery 3, 711-715, 2004

Improving safety evaluation means that drugs with better benefit / risk ratio and a greater likelihood of success will be developed more efficiently.

Improving safety evaluation will lead to a reduction of adverse drug reactions, more rational and probably also reduced use of experimental animals, more adequate regulatory requirements and shortened duration of drug development. This will be aligned with the EFPIA policy concerning the use of animal in R&D (Appendix 2).

There are basically two different approaches to 'Predictive Toxicology':

- Basic paradigm of safety evaluation is to predict a safe starting dose for the Entry into Human (EIH) study, potential adverse effects (target organs, cellular targets) in the patient under treatment and an acceptable therapeutic window i.e. a range of doses where therapeutic benefit occurs in the absence of unacceptable adverse effects,
- Ranking process in candidate selection during discovery. Early / predictive safety testing can include in *silico* methods, the 'omics technologies, genotoxicity, reproduction toxicity; in vitro toxicity, investigation of potential metabolites (and their toxicity) and in vitro safety pharmacology.

The process of improvement of predictivity of safety evaluation can be reached preferably by an international collaborative approach. InnoMed should establish a network of scientists who will:

- Collect information on currently available expertise, experience and methodology,
- Profile the focus and main directions of activities,
- Consult with potential academic and biotech partners on the best approaches to reach the desired goals,
- Define the agenda for future research based on inputs received from the different companies and additional inputs developed in collaboration with all stakeholders.

To achieve these goals the following stakeholders are to be involved:

- European-based, research-intensive pharmaceutical companies which have already considerable knowledge in the fields of classical toxicology and 'predictive' toxicology,
- Small and Mid-sized Enterprises (SME) with expertise in the disciplines needed (e.g. software-developer, data-base provider; chip producers and other technology manufacturers),
- European University Laboratories with focused expertise,
- European Regulatory Agencies,
- The Health Environmental Sciences Institute, who have started an initiative on non-clinical/clinical safety correlation,
- Working group from the InnoMed consortium members (Education & Training; Knowledge Management) and experts from EUFEPS,
- The Toxicogenomics working group from the InnoMed consortium member EFPIA companies,
- Representatives from patient groups.

2.2.2 Clinical Safety and Pharmacovigilance

Pharmacovigilance is the science and activities related to the detection, monitoring, assessment, understanding, prevention and treatment of adverse events or any other safety related issue associated with drug administration[16].

The current process of spontaneous reporting of adverse events has a low rate and often provides insufficient relevant information on cases and of their follow-up, not enabling a proper assessment. Such data are also reported inconsistently depending on geographical and cultural considerations. The risk associated with a new drug is difficult to quantify due to two factors:

[16] WHO 2002. The Importance of Pharmacovigilance – Safety Monitoring of medicinal products. ISBN 92 4 159015 7

- There is no known denominator to relate the number of events and patients against (no real global database is available to better understand the natural evolution of the disease), as is the case in clinical trial settings and,
- The inappropriate differences in reporting similar events e.g. symptoms versus diagnoses.

Hence relating risk to benefit is difficult because of the absence of a denominator and of difficulties to perform a proper assessment linked to the quality of the data. The current process of reporting safety information to Health Authorities has resulted in a huge bureaucratic "treadmill" whereas the resources required in industry and Health Authorities are by no means commensurate to the effectiveness and benefits of the current safety management process. Safety issues, such as the recent product withdrawals, demonstrate weaknesses of the pharmacovigilance process and the need for improvement and new tools (such as risk management).

There is an urgent need for a more pan-European approach to pharmacovigilance on the path to a global approach. Therefore, the Innovative Medicines Initiative recommends the development of new tools for capturing and monitoring adverse events and to produce a global adverse events database as compared to restricted local data bases (national, WHO, etc).

In the EU, electronic capture of clinical data combined with electronic data capture of prescriptions is already routine in some countries, such as Sweden, where 90% of outpatients' clinics are already computerized.

The objective is to leverage the information existing in different systems at the global level in order to consolidate relevant information, and to develop expert systems that can help to identify signals This will allow moving away from the current pharmacovigilance system based on the management of information submitted in a haphazard manner by health care professionals and consumers, to the active and automated retrieval of information collected in clinics routinely and its processing by means of a risk-based algorithm.

A next, desirable step will be the integration of non-clinical and clinical safety data.

This effort needs to be co-ordinated with the knowledge management group and the proposal is to set up a task force with the EFPIA Science Technology Regulatory Policy Committee (STRPC) on Pharmacovigilance to develop an action plan on how to address the issues mentioned above.

2.3 PredTox Project in the 6th Framework Programme

There have been significant advances in four areas of technology that could deliver improved prediction of compound induced toxicities. These technologies include:

- *In silico* tools to aid the detection and prediction of specific toxicities,
- Toxicogenomics, i.e. detecting changes in gene expression in cells (determined by mRNA measurements) in response to exposure to a toxic compound,
- Toxicoproteomics, which is the detection of abnormal patterns of proteins in cells in response to exposure to a toxic compound,
- Metabonomics, which is the detection of changes in endogenous cellular metabolism of a cell or organism. As per the technologies above, the context is determining changes in endogenous metabolites in response to exposure to a toxic compound.

Since the 'omics technologies result in the generation of huge volumes of data, it is mandatory to carry out parallel research in bioinformatics/knowledge management and IT, technology development to allow key changes in the measured experimental parameters to be identified.

The main purpose of the PredTox Project funded in FP6 is to evaluate the utility of these new technologies in preclinical safety testing and provide a functional database containing integrated information from the 'omic technologies with that from traditional toxicity endpoints for liver and kidney toxins. Once established the challenge will be sharing the application of these technologies in preclinical safety testing and training and educating scientists from industry and in the Regulatory Authorities in their use and value.

There is a need to identify how much expertise and experience in the use of these technologies, as applied to toxicology, is currently available within Europe and to share this information between the different stakeholders.

The ultimate goals must be to:

- Assess the value of combining results from 'omics technologies together with the results from more conventional toxicology methods in more informed decision making in preclinical safety evaluation,
- Initiate and support the development of scientists within the novel field of Systems Toxicology,
- Critically review the value of this approach together with Regulatory Authorities and finally agree upon the approach for their use.

2.4 The European Centre of Drug Safety in the 7th Framework Programme

Based on workshops with experts from all the mentioned stakeholders on non-clinical safety, a priority proposal for future safety evaluation under a European Technology Platform (ETP) was developed for implementation during the 7th framework programme (FP7). The most urgent need identified by this group to help achieve the goals above is to bundle, and optimally organize all related predictive toxicology activities as a nucleus for harmonization. This new structure should be named "The European Centre of Drug Safety" or ECDS, which initially will focus on non-clinical issues.

Subsequent discussion emphasized the necessity to integrate Clinical Safety and Pharmacovigilance into the activities of the ECDS. A detailed analysis on the specific needs and requirements is ongoing and details on priority programmes have to be extensively profiled in the near future.

The European Centre for Drug Safety will be an independent centre composed of a limited core group with a wide network of academics, industry scientists and regulators. The goal will be to promote safety sciences with a focus on human pharmaceuticals by means of:

- Supporting and proactively driving research that improves and innovates drug safety assessment, involving EU academic centres, the pharmaceutical industry and regulatory authorities, e.g. development of databases including knowledge management tools for data analysis in pharmacovigilance.
- Providing leadership and supporting professional education & training,
- Providing communication on drug safety issues to stakeholders / media and,
- Compiling and maintaining a safety data warehouse as an essential activity to support the other three areas,
- Improved healthcare provider training in the detection of adverse drug reactions (ADRs),
- Improved communication between patients, physicians and other healthcare providers on the risk and benefits of medicines.

Following an analysis of the activities of other organisations in the European Union and United States with an interest in drug safety, it became evident that no existing organisation meets the above remit for the proposed European Centre for Drug Safety. The figure below shows a list of the main organisations / stakeholders in the European Union (and United States) involved in the Drug Safety Evaluation Process.

ILSI/HESI	Drug Information Association - DIA
Societies of Toxicology (ETS / BTS) other member states' societies	Societies of Toxicological Pathology (ESTP / BSTP / ESTP)
Academy of Medical Sciences UK	EFPIA / ABPI / LEEM and other member EU states' organisations
European Federation for Pharmaceutical Sciences – EUFEPS	Other safety research-related professional societies
Centre for Medicines Research International – CMR UK	American Association of Pharmaceutical Scientists - AAPS
Fund for the Replacement of Animals in Medical Experiments – FRAME	Institut National de Recherche et de Sécurité - INRS Fr

Europ. Centre for the Validation of Alternative Methods – ECVAM	European Medicines Agency - EMEA
European Commission	EU Health Authorities and Health Department
Any identifiable patient groups	Deutsche Forschungs Gemeinschaft (DFG) D
Any identifiable media organisations	
Academic centres of excellence in safety sciences	Surrey/Birmingham Uni – MSc program

Figure 8: Organisations involved in the Drug Safety Evaluation Process

The Centre would have limited permanent staff but would have the benefit of a European wide network of preclinical experts. There are well-established organizations (e.g. CMR International and HESI models; run by group of <6 people) that would exemplify that such a model would suit the ECDS.

The Centre must be independent and should consist of:

- A scientific advisory board (members nominated by EC, Pharmaceutical Industry, academia, and regulatory authorities),
- A director (senior safety scientist),
- Project managers (projected number: 8; including pharmacovigilance),
- Data mining/IT support personnel (projected number: 5; including pharmacovigilance),
- The Centre will have 2 Sections: Non-clinical Safety – Predictive Toxicology and Clinical Safety and Pharmacovigilance.

Regarding overall governance of the Innovative Medicines Initiative, it is referred to in Chapter 10, "Implementation" of this document.

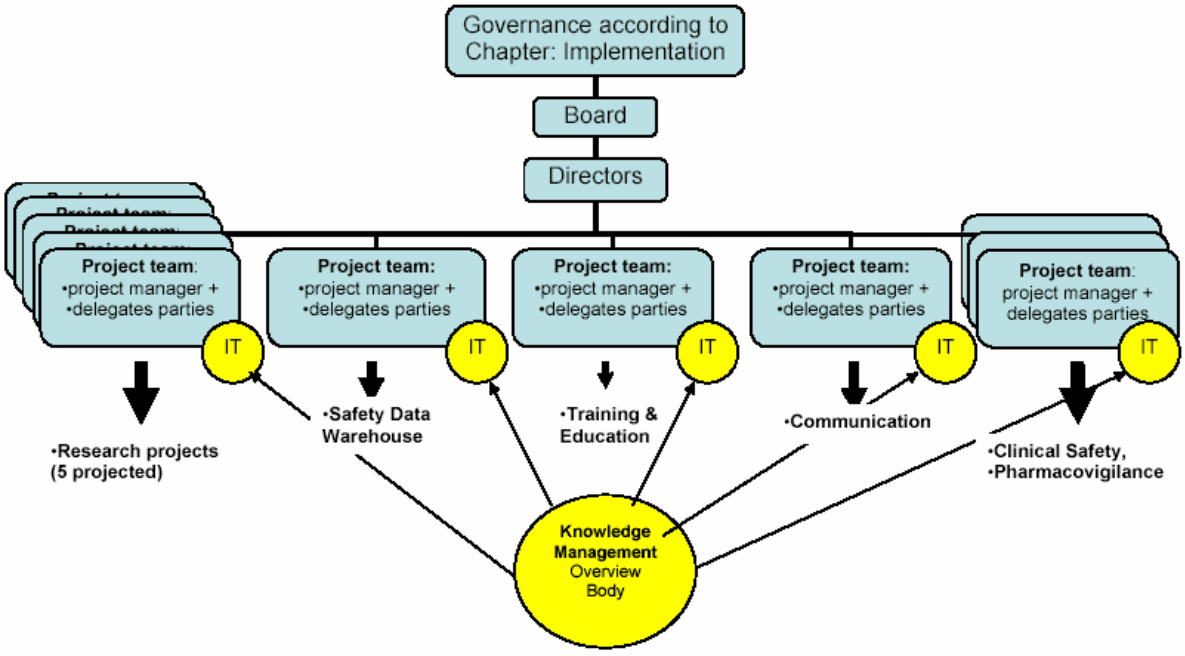

Figure 9: Structure of the ECDS and interaction with knowledge management

The ECDS should be located adjacent to an organisation with a good IT infrastructure.

The focus of the ECDS activities will be on non-clinical safety research. However, since the overall aim of the activities will be to improve safety of drugs in humans there is an obvious interaction with the clinical

area. Therefore the dependency on human data has to include input from clinical safety and pharmacovigilance.

The ECDS will start up with 11 envisaged projects. Eight of these will be maintained on a permanent basis, i.e. communication, education, the safety data warehouse and 3 projects on pharmacovigilance. Research projects per year will be initiated and supported on a temporary basis. In principle each of these projects will be managed by a project team consisting of a project manager (ECDS staff) and a number of delegates appointed by the various stakeholders.

Based on current needs and to give direction to the ECDS research activities part, the projected Research Projects are already defined in this proposal (see below for details). When the demand for additional projects exceeds the projected number, the total number of Research Projects can be increased.

A number of these activities can be started directly after the ECDS becomes operational. Other additional and follow-up projects will be defined and initiated by the activities of the ECDS itself.

To facilitate a fast response, in terms of initiating research and addressing emerging general drug safety issues, the ECDS will also give advice on 'grant applications' / decide on tenders for research proposals from FP7 and other proposals. The ECDS will be a long-term activity (>10 years). The parties involved will evaluate performance with cyclic reviews.

There should be "quick wins" through improvement of active communication and measures regarding education.

The mid- and long-term metrics of success would be:

- Research Projects: the number of research projects operational within 2 years. This should be faster in comparison to conventional methods. This is of particular importance since it would allow action to be taken quickly and adequately on emerging general problems regarding drug safety,
- Number of students included in educational courses,
- Number of projects initiated based on results of the database after the first 4 year period,
- Successful development and implementation of safety models with improved predictivity.

2.4.1 Role of the ECDS in Research

In order to get safer drugs faster, improved and innovative testing paradigms are required. These can only by obtained by investing in research; therefore the most important focus of the ECDS has to be the initiation and proactive drive of safety research. The approach will be:

- Identifying research needs in safety sciences and implementing and coordinating research programmes (science board),
- Catalysing increased collaboration between industry / regulators / academia / other stakeholders,
- Provision of an umbrella for any FP7 project (e.g. extension of the FP6 PredTox activities) and,
- Giving advice on 'grant applications' / decide on tenders for research proposals from FP7 and other proposals.

The safety data warehouse is considered an essential, undeniable tool in identifying and supporting research activities in the indicated area. The specific role of this tool will be further described in the relevant section of the proposal.

The strong links to "Knowledge Management" are evidenced by the fact that IT support is to be integrated into each and every individual project.

Based on current needs a number of important research projects have already been identified. Since it will be the aim of the ECDS to run such research projects these proposals have been implemented already in this proposal (see below). The advantage will be that these projects can be directly initiated by the ECDS during the build up period of the safety data warehouse. The safety data warehouse is the tool that should support the definition of additional important research areas.

Following intense discussions the two pillars of ECDS research activities may be:

- Framework for biomarker development,
- Relevance of non-genotoxic carcinogens.

These research areas are felt to be of key importance for improving the predictivity of drug safety evaluation. Please see below for further details.

Furthermore there are very important research needs that should be dealt with immediately after the start of the ECDS as Individual Research Projects of Priority:

- Development of in silico methods,
- The issue of intractable toxicities.

2.4.1.1 Framework for Biomarker Development

Within the ECDS a European framework for the development of safety biomarkers will be created, including platform / guidance for technology harmonization, validation, data coherence and bio-informatics.

The main objective of this Research Project is development and validation, not identification of biomarkers. The identification of new biomarkers should (primarily) be carried out by different parties (industry; academia; EU Integrated Projects or as individual projects of the ECDS).

These activities should help especially the exploitation of the extended FP6 liver & kidney study (PredTox part of InnoMed program) for biomarker identification.

A proliferation of candidate biomarkers and surrogate clinical endpoints is expected in the coming years driven by -omic technology (proteins, metabolites, individual gene expression and perhaps gene expression signature patterns).

The purpose of the project is to clarify the utility and human relevance of these candidate biomarkers and in consequence their regulatory value.

The characteristics of the perfect (preclinical/clinical) biomarker for monitoring toxicity are as follows:

- Specific for certain types of injury
- Indicates injury in a variety of experimental species as well as humans
- Can be used to bridge across non-clinical/preclinical studies to clinical and surveillance types of studies
- More effective at indicating injury than any other biomarker currently used
- Used instead of classic biomarkers, not in addition
- Can be easily measured (in real time) even at a „later“ stage (not time critical)
- More reproducible, sensitive and measurable than the toxicity endpoint itself
- Reduces number of individuals tested (animals or humans).

The overall strategy is to influence, support, work with and build on existing programs and EU projects (e.g. PredTox part of InnoMed program; other EU FP6 IP programmes) and the ILSI/HESI Biomarker subcommittee.

Each new candidate biomarker requires validation in the preclinical and clinical arenas and the minimal biomarker pre-validation package prior to acceptance is shown in the figure below. To achieve general acceptance in-house validation is not sufficient (as shown in the past for the development of *in vitro* tests,). Therefore collaboration between several stakeholders (academia, industry, regulatory authorities) is essential for a proper validation procedure, thus making this a pre-eminent subject for an ECDS Research Project.

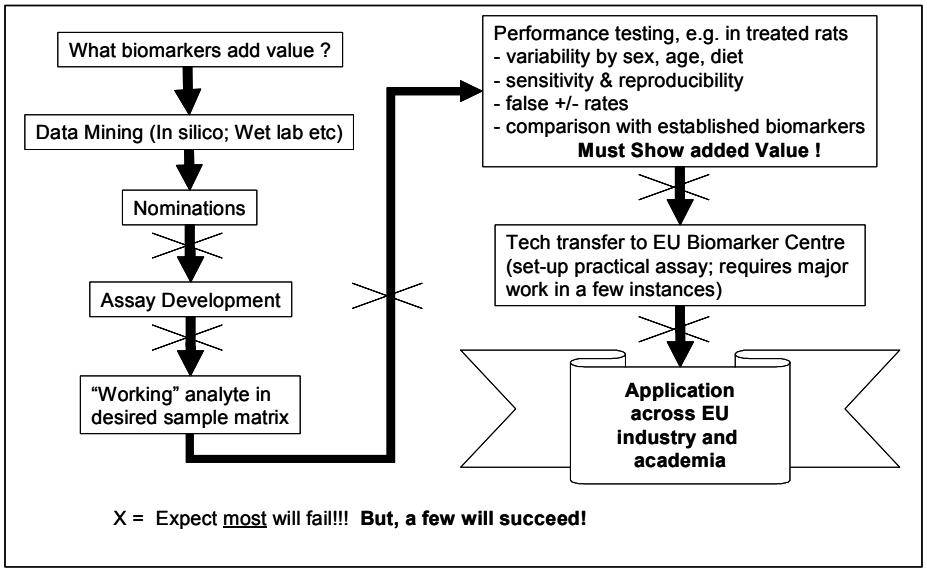

Figure 10: Minimal biomarker pre-validation prior to acceptance

Implementation within the ECDS will be as for any other Research Project, i.e. the development of an individual biomarker (or a limited set of directly linked biomarkers) will be allocated to a project team as described above. Thus depending on the number of candidate biomarkers identified a number of Research Projects will be initiated. A separate Biomarker Strategic Management Team composing of selected members and project managers from the individual Research Projects will have the task to prioritize, accept, reject and cancel individual biomarker development projects.

Depending on the stage of development of a specific marker the Research Project Team will support a number of activities:

- Define transparent criteria for acceptance,
- Kit development for different species,
- Validation of acceptable criteria in preclinical species,
- Validation in sufficient number of clinical studies,
- Mechanistic understanding,
- Data analysis.

This requires extensive work that exceeds the resources of individual institutes or companies and it is not the core business of pharmaceutical companies

Metrics of Success and duration of the project:

- The 'quick wins' will be identification and consensus of a list of promising biomarkers, while the identification, consensus on data package needed to support acceptance of a biomarker and completion of this data package for individual biomarkers can be expected as mid- and long-term measures of success,
- The duration of the project may be >10 years with cyclic reviews of performance by parties involved.

2.4.1.2 Relevance of Rodent Non-genotoxic Carcinogens

About 50% of rodent carcinogenicity bioassays show a treatment-related increase in incidence of tumours (in most cases these are indeed through non-genotoxic mechanisms, but there are only about 20 known human carcinogens, most of which are genotoxins.

Substantial industry and regulatory resources are spent in unravelling irrelevant findings in rodent carcinogenicity assays.

Greater understanding in this area, derived from the application of new technologies, would provide considerable benefits for efficient drug development.

An issue of current high priority is receptor-mediated carcinogenesis as e.g. demonstrated by the peroxisome proliferator-activated receptor (PPAR) carcinogenicity issue.

The possibility that the therapeutic and the rodent tumorigenic effects are driven by the same mechanism cannot be ruled out in many cases.

A better understanding of the mechanisms of receptor-mediated carcinogenesis will contribute to the definition of the human risk associated to their use and give support to risk management analysis.

The scope of the research activities is:

- Application of mechanistic studies, -omics approaches to development of predictive markers for non-genotoxic carcinogenicity,
- Evaluation of alternative approaches, e.g. alternative carcinogenicity studies of shorter duration or sub-chronic studies in aged animals or use of transgenics with altered or deleted relevant receptors,
- Understanding species differences.

The final goal of this project will be to develop more predictive and if possible shorter testing paradigms with respect to identifying human carcinogens.

In order to understand better the relevance of rodent studies for prediction of human carcinogens the following scientific approach will be used:

- Mechanistic studies for providing the understanding of the human relevance of identified hazards, e.g. receptor sub-typing, distribution, species differences, involvement in cell proliferation, nutritional interactions, cellular pathways / cell-cell interactions and secondary messengers,
- Developing new general assays *(in vivo / in vitro* /-omics) or refining existing ones for early identification of potential hazards (through validation and standardisation). These might include but are not exclusive to alternative carcinogenicity studies of shorter duration or sub-chronic studies in aged animals or use of transgenic models with altered or deleted relevant receptors.

Metrics of success and duration of the project:

- Progress in addressing the safety issues related to e.g. PPARs would be greatly accelerated,
- Number of useful biomarkers (including clinical use) will become available as a result of mid- and long-term success, and finally the reduction of numbers of 2-year bioassay that may result.

Although research in this field will be performed by Academia and Industry, it is essential that Regulatory Authorities be involved in the assessment of results and recommendations for additional research. Moreover the availability of data as can be provided by the safety data warehouse may be an essential asset contributing to the success of this project.

2.4.1.3 Development of in silico Methods

There is very important research need on the development of in silico methods, which should be dealt with immediately after the ECDS becomes operational as an Individual Research Project of Priority in order to:

- Improve predictivity for endpoints characterized in late non-clinical safety studies e.g. chronic target organ toxicity; reproduction toxicity),
- Provide tools to Screen and select best chemical lead at Discovery stage,
- Avoid specific structural (and activity) characteristics linked to safety issues,
- Judge on «Toxicodevelopability» in very early development,
- Help to tailor a specific toxicity testing program.

2.4.1.4 Intractable Toxicities

There is a very important research need to tackle intractable toxicities. This should be dealt with immediately after the start of the ECDS as Individual Research Project of Priority.

Intractable toxicities represent issues as described hereunder and are characterized by the fact that they occur in humans and were not predicted by non-clinical findings and vice versa. Since part of the research (e.g. drug hypersensitivity) may be initiated from the clinical side working backwards to non-clinical models it is also expected that the safety data warehouse may play a key role in making this an ECDS research project par excellence. This research project should be initiated when the ECDS becomes operational. Scope of the project is to:

- Select a few high impact areas that are currently causing repetitive delays or compound terminations, e.g. Testicular toxicity; biliary hyperplasia / hepatotoxicity; vasculitis; phospholipidosis; hypersensitivity,
- Address the selected issues by e.g. new animal models, cellular models / stem cells / others, human tissues, imaging; fundamental biology and modelling.

The funding should be targeted based on specific expectations and urgent needs.

2.4.2 Role of the ECDS in Education & Training and Communication

It is of key importance to ensure available workforce in drug safety evaluation for future. Some of the key tasks of the ECDS will be:

- Close co-operation / co-ordination with 'FP7 Training & Education Workpackage',
- Identify existing best practice and coordinate and extend to other regions, e.g. extend UK CPD - Continuing Professional Development to rest of Europe or Surrey MSc model (initial level) and higher level CPD,
- Map existing EU Member States training of workforce in safety sciences,
- Identify centres of excellence to deliver training and education,
- Developing a EU curriculum in safety sciences including EU credits for CPD,
- Accreditation of "safety scientists" in drug safety,
- Support of job rotations to other areas of safety science to allow the quicker spread of relevant expertise,
- Address the issue of shortage of expertise e.g. of toxicological pathologists, system biologists and animal technicians.

There are advanced ideas and elaboration on the topic available from EUFEPS, which will be used in the beginning.

Communication: Current negative public opinion regarding pharmaceutical companies underlines the need for communication with media, patient organizations, professional interest groups and the public, to explain Good Practices of use of drug safety data and more in general for a better public understanding of the issues: what can and cannot be expected of drugs with respect to safety. The ECDS can play an important role in providing information and education regarding these issues.

2.4.3 Role of the ECDS in Knowledge Management

The efficiency of drug safety evaluation will be increased by closer international co-operation on data management and data sharing. Optimal data management will provide a sounder basis for decision-making, reduced cost and time of drug development. The key role the safety data warehouse can play is already exemplified above. It will additionally contribute to a positive public image of safety research. The role of ECDS is:

- Close co-operation/co-ordination with 'FP7 - Knowledge Management Workpackage',
- Collection, reference, validation, quality control (QC), maintenance, search of data, data mining, reporting including taking care of "negative" results which normally are not published by scientific

Journals, but can be of great value in several areas and also help with reducing unnecessary animal testing,

- Definition of boundaries of databases – nature/level of data and organisation of data sharing between industry companies; specific issues of competition and proprietary information to be managed; (Possible incentive: extension of exclusivity?),
- Identification of areas to focus on e.g. excipients, all data from GLP toxicity studies (conventional endpoints such as clinical pathology, haematology and pathology),
- Inclusion of data on all new drugs – prospectively, on marketed drugs depending on issues, on terminated compounds and of clinical safety data as available,
- Inclusion of anonymised data by pharmacological class or include structural info if feasible,
- Clarification and management of access rights and restrictions of access to certain levels of data,
- Safety data warehouse management and maintenance.

2.4.4 Role of the ECDS in Clinical Safety and Pharmacovigilance

A detailed analysis on the specific needs and requirements are ongoing and details on priority programmes have to be extensively profiled in the near future. The main topics are identified as follows:

- Improve healthcare provider training in detection of adverse drug reactions (ADRs),
- Development of databases including knowledge management tools of data analysis in Pharmacovigilance,
- Improve communication between patients, physicians and other healthcare providers of risks and benefits of medicines.

The resource figures given below are rough assumptions at the lower range for activities in this field when comparing the relation of non-clinical versus clinical budget figures of the drug development process in general.

2.5 Resources

ECDS – Project support and management	€ per year
Staff: 1 Director, 8 Project Managers, including *Pharmcaovigilance*, 5 IT- Support, including *Pharmcaovigilance* (€ 2'800'000) Meetings: 1 Project manager and 14 delegates at € 2000 (€ 28'000) Meeting facilities etc. (€ 5'000) 4 Meetings per year of 8 different project teams (Sum: € 1'120'000) Subtotal fix costs (incl. 20% Overhead):	4'700'000
ECDS – Project-related costs Subtotal for 2 priority projects: Costs per project: € 7'500'000 ("Development of *in silico* Methods" and "Intractable Toxicities") Subtotal for average 3 projects (Costs per project: € 5'000'000)	15'000'000 15'000'000
ECDS – Communication	1'000'000
ECDS – Education	1'000'000
Costs per year directly related to the ECDS	36'700'000

Biomarker Development	
Project support and management - Fix costs: 3 projects / person = maximum 18 projects	3'000'000
Project-related costs Costs per project: Analytical work-up in 50% of projects, Performing cost supported by Labs, (Selling point to companies), Data analysis (ballpark figure: € 100'000), Workshops and follow-up activities, education, etc.	500'000 - 1'000'000
Subtotal for fix costs and projects:	15'000'000
Extension of FP6 liver & kidney study for ~10 substances	7'500'000
Costs per year	22'500'000
Relevance of Non-genotoxic Carcinogenicity - Mechanistic studies	
Fix costs: 50 'Post Doc' positions at € 150'000 / position)	7'500'000
Studies of Alternative Models Subtotal for projects: 20-40 GLP-compliant chronic rodent studies at € 500'000 per study. Based on the cost of ILSI-HESI transgenic mouse project. Actual calculation based on 30 studies	15'000'000
Costs per year	22'500'000
Clinical Safety and Pharmacovigilance	
Improve healthcare provider training.	22'900'000
evelopment of databases and knowledge management tools	22'900'000
Communication between patients, physicians and other healthcare providers	22'900'000
Costs per year	68'700'000
Summary of Resources Needed	
Costs directly related to the ECDS Including Projects: "Development of *in silico* methods" and "Intractable Toxicities"	**36'700'000**
Biomarker Development	**15'000'000**
Extension of "PredTox" from FP6	**7'500'000**
Relevance of Non-genotoxic Carcinogens	**22'500'000**
Clinical Safety and Pharmacovigilance	**68'700'000**
IT Infrastructure and support (based on experience ~10% of above)	**15'000'000**
Total costs per year	**165'400'000**

2.6 List of contributors

Follow-up Meeting to Safety Workshop

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Additionally to the above, during the initially held **Safety Workshop** the following experts contributed:

Mr. Paul Barrow, MDS, F
Dr. Karima Boubekeur, for EFPIA
Dr. Jacqueline Carleer, Lilly, B
Dr. Björn Dahl, AstraZeneca, S
Dr. Bengt Danielsson, MPA, S
Prof. Anthony Dayan, Univ. of London (em.), UK
PD. Dr. Karin Fattinger, University of Zurich, CH
Dr. Nicolas Grandjean, for EFPIA
Mr. Antonio Guzmán, Esteve, E
Dr. Michael Holsapple, ILSI/HESI, USA
Dr. Niels Krebsfaenger, Schwarz Pharma, D
Dr. Mathias Locher, Micromet, D
Dr. Maurizio Mariani, Serono, I
Mr. Alistair Newton, EFNA
Ms. Irene Norstedt, European Commission
Dr. Klaus Olejniczak, BfArM, D
Prof. Josef Pfeilschifter, University of Frankfurt, D
Dr. Benno Rattel, GPC Biotech, D
Prof. Rolf Schulte-Hermann, Univ. of Vienna, A
Dr. Hermann Schweinfurth, Schering, D
Dr. Thomas Singer, Roche, CHE
Dr. Torben Storgaard, NovoNordisk, DK
Prof. David Tweats, University of Wales, UK
Prof. Spiros Vamvakas, EMEA
Prof. Jan Willem van der Laan, RIVM, NL
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3 Improved Predictivity of Efficacy Evaluation

3.1 Introduction

Advances in knowledge and technology have greatly increased our expectations of improved healthcare. The investment into R&D of new medicines has seen spectacular growth over the past decade. Despite technical progress in drug discovery technologies, there has not been a concomitant increase in R&D productivity. The current developments in the basic discovery sciences have not been mirrored by concomitant progress in understanding the clinical basis of disease and therefore the development of novel effective therapies. This situation needs to be addressed and a better-integrated approach to innovative medicines R&D is required.

The objective of the Innovative Medicines Initiative is to accelerate the process of bringing new medicines to market and to increase the efficiency of drug development. This chapter will provide a framework of recommendations and inputs for enhancing predictability of success by focusing on the relevant bottlenecks in the drug discovery and development value chain (Figure 4, page 11). For this purpose, the major bottlenecks have been grouped into four key areas; pharmacology, biomarkers, patient recruitment and regulatory approvals.

It should be remembered that the benefit of a new drug to the patient and its approval involve, of course, not just its clinical activity but also its safety. Several of the bottlenecks defined in figure 4 apply to both of these aspects, and come together in the risk/benefit analysis of the regulatory approval process and in post-marketing pharmacovigilance. The detailed analysis of safety is presented in Chapter 2 of this document.

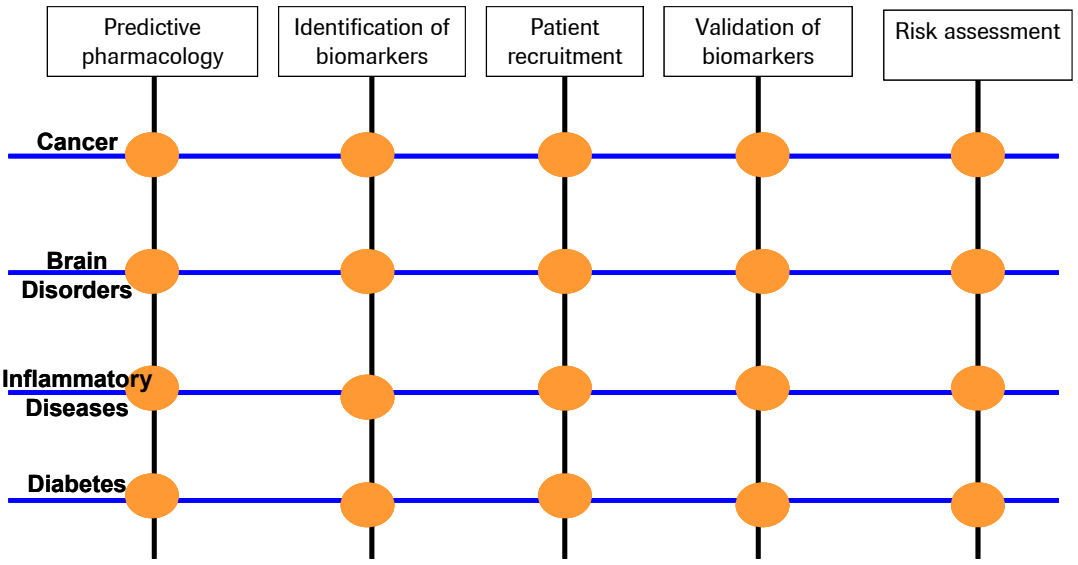

Figure 11: Efficacy and Safety are often disease specific

Following an extensive consultation process, this SRA is focussed on the following disease areas:

- Cancer,
- Brain disorders,
- Inflammatory diseases,
- Diabetes.

These diseases have been chosen because they are first and foremost important areas of unmet medical need, affecting the lives of millions of European citizens. We do realise, however that there are many other medical conditions that the SRA could also have addressed which remain problematical in our society.

These four were chosen because the opportunity exists through this Technology Platform to address challenges that have so far prevented or impeded progress in the development of better treatments, and to encourage research which we predict will have real impact within the time frame of this programme. In other words, significant progress in these areas is expected if the SRA is implemented. Although there are elements that are common to all four therapy areas, and in fact may be common to other medical conditions also, each disease has a unique combination of issues: for one it might be the lack of predictive animal models in which to test putative treatments; for another, it might be the heterogeneity of the patient population and the inability to recruit the right patient group for clinical trials; for a third, it might be the failure to consider quality of life measures in the demonstration of clinical efficacy and inadequate attention being paid to patient needs. Addressing these issues in the context of one major disease therefore informs others and provides a framework for change that will improve and guide the drug discovery process for all disease areas. This will be particularly powerful if the science to be undertaken is able to streamline the clinical trials and regulatory processes reducing not only failure rates, particularly in late clinical development, but also the time and cost. Such a sea change in the business would greatly encourage research into other diseases particularly those that have been hitherto neglected on the grounds of the high cost of R&D.

This chapter describes how academic clinical and pharmaceutical expertise can be brought together to identify the needed biological tools, and to advance the use of emerging technologies including 'omics and imaging that will be required for their successful implementation. Multidisciplinary groups with expertise in each of the four disease areas reviewed the current state of knowledge and outlined a strategy to address the key bottlenecks in drug discovery. These are detailed below. However, it has become clear from the series of workshops on efficacy bottlenecks that there are overarching needs, common to all disease areas, which illustrate the challenges of improving efficacy such as to:

- Develop better understanding of disease mechanisms,
- Develop in vitro and in vivo models predictive of clinical efficacy,
- Develop in silico simulations of disease pathology,
- Stimulate translational medicine in an integrated fashion across industry and academia,
- Create disease-specific European Imaging Networks for establishment of standards, validation of imaging biomarkers and development of regional centres of excellence,
- Create disease-specific European Centres for validation of "omics-based biomarkers",
- Co-ordinate the development of national patient networks and data bases to develop a true pan-European organisation for patient selection and clinical trial analysis,
- Form a European stakeholder consortium to address value demonstration, including quality of life issues, patient reported outcomes and burden of disease,
- Develop a partnership with regulators to devise innovative clinical trial designs and analyses, to aid acceptance of biomarkers and to promote data sharing and joint consideration of ethical issues.

3.1.1 Pharmacology

While infectious diseases remain a major threat to the health of Europe's citizens, the challenges to an aging population are the chronic, degenerative diseases. Many of our approaches for chronic diseases focus on control of symptoms, and novel drug development should be targeting treatments that affect disease progression and ultimately, cure it. Basic science advances in the last few years have indicated that most common diseases entail extremely complex patterns of pathogenesis, involving the regulation of dozens or even hundreds of genes and their protein products. In the light of advances in genomics, proteomics, and bioinformatics, basic science of the 1980s and 1990s where single or few pathways were investigated would currently seem naïve at best.

New treatments will therefore only emerge from a better understanding of the pathophysiology of disease. This work will not only point the way to treatments with more predictable efficacy, but will also create the biological tools to facilitate the drug discovery process, and the diagnostic agents needed for early detection of the disease. These biological tools are needed to allow a rational and well-informed choice of molecular target, for the development of in vitro screening methods to discover promising drug leads, and for animal models that demonstrate pharmacological action and predict efficacy in the human disease. These are not trivial undertakings and past inadequacies in this regard are responsible for a significant proportion of the drugs that have failed in clinical trials to meet their endpoints.

A major key to reducing attrition is the development and use of preclinical models that are more predictive of efficacy and safety in clinical trials. In order to enhance the predictive ability of preclinical models, we must utilise technologies and endpoints that most closely reflect those that are or could be used in clinical trials. Potential new therapies are frequently reported yet most of these exciting new discoveries never advance beyond the laboratory bench. A critical component to the successful deployment of translational medicine research in drug development to deliver these new drugs is the focus that must be given to comparative medicine, physiology and pharmacology. For many diseases, we have an imperfect understanding of the relevance of preclinical experiments and their relation to clinical experience. Relevant animal models as well as early predictive clinical endpoints are needed to allow a wider testing of novel hypotheses. Key to this is the development of comprehensive disease lifecycle models that directly link the rationale in preclinical modelling to the treatment of clinical disease. Further, developing, refining and validating complex animal models that directly link therapeutic targets to the phenotype of disease (confidence in rationale) and developing and refining animal models of toxicity that allow earlier prediction of human response to drugs and identification of safety biomarkers (confidence in safety) are key enablers to successful translational medicine research in drug development. In order to enhance the predictive ability of preclinical models, technologies and endpoints should be utilized that most closely reflect those that are or could be used in clinical trials. This will encourage technology transfer in both directions, that is, technologies and biomarkers that are currently used in clinical trials can be more directly adapted to preclinical models and novel technologies and biomarkers being developed in animals may be efficiently validated and introduced to clinical trials.

A critical need will be access to human tissue banks and biobanks linked to medical records containing information on phenotype. This will be essential for understanding the link between molecular targets for drug intervention and the fundamental pathophysiology of disease, for testing and validation of biomarkers, and for translating the results of clinical trials into a molecular understanding of responsiveness and side effects. European-wide co-ordination of existing national efforts is crucial to establish common standards, definitions, diagnostic criteria, protocols, data standards and data mining tools etc. The organisational effort will be considerable and will need to encompass in addition, the ethical, legal and societal issues around ownership, consent and confidentiality of the data.

Better understanding of disease pathophysiology will provide the basis for the predictive pharmacology that is essential to reduce attrition rates in clinical trials. A key output of this research will be the discovery and validation of biomarkers, which are seen as absolutely critical to the success of modern drug discovery.

3.1.2 Biomarkers

A biomarker is defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’[17]. Biomarkers are quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness. They can provide new insights into a drug’s mechanism of action, metabolism, efficacy and/or safety and into disease mechanisms and disease course. They can play multiple roles during the research and development phase of a drug. Biomarkers can be used as tools to understand the biology of a disease but also to understand the effects of a new drug. Biomarkers may also provide information on patient sub-populations that might respond to a new drug or be susceptible to side effects. This approach is known as patient stratification and is the basis of the future concept of personalised medicine.

The value of biomarkers is that they hold enormous potential to point us in the direction of critical information for developing better diagnostics and drugs, and for helping the industry to manage the innovation process in a more cost-effective manner. Thoughtful and proactive use of biomarkers can improve the mechanistic information generated in drug development, allowing a better understanding of the sources of variation and the correlation between discovery, preclinical and clinical information. This will result in better early decision-making, reducing late-stage and more costly attrition. With the deployment of validated biomarkers, one could expect better clinical study designs in more suitably defined populations with endpoints yielding improved labelling and marketing information. In short the application of biomarkers in the drug development process will translate into such benefits as: increasing the probability of program success and reduced cycle times, matching patients with therapy; faster optimisation of therapy; improved compliance with therapy; reduced complications of therapy and disease; more efficient drug development; more effi-

[17] Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," Clinical Pharm. & Therapeutics, vol. 69, N. 3, March 2001

cient healthcare delivery; & ultimately reduced societal healthcare burden. Furthermore, the identification of diagnostic biomarkers will be essential for improved early intervention in disease and will be a key technology in the development of more focused drug prescribing. However, the vision will only be achieved if there is the right approach to optimization of biomarker investment, performance, and application and this is a core deliverable of translational medicine research.

The issue is how to validate biomarkers. This is a very lengthy and expensive exercise involving many patients and years. The FDA has proposed different steps in the validation process but there is no real consensus among all partners. For example a validated biomarker is defined as 'a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results'. Proper validation is essential if biomarkers are to develop from being tools for internal use by the pharmaceutical industry to measures that can be used to drive approval decisions.

The successful development of biomarkers and their integration into the drug discovery process also requires the development of current technology and improved access to it. The use of genetic variables for patient stratification is in its infancy in many therapeutic areas but there is already an emerging literature and clinical evidence on the power of pharmacogenetics to predict efficacy as well as side effects. The 'omics technologies are seen as essential for the discovery of accessible biomarkers (e.g. in blood, urine or cerebrospinal fluid) for diagnostics, disease progression, prediction of treatment outcome, and measurement of treatment effectiveness.

The other essential technologies are the bio-imaging methods such as MRI or PET. As with other biomarker methods, the development and validation of imaging biomarkers in animals is an important precursor to the use of such techniques in man. There is a need for further refinement to the technologies such as improvements in resolution, sensitivity and comparability, and a pressing need for greater access of patients to centres of excellence in imaging methods.

For this to happen, standards and registries of biomarker and clinical data will need to be agreed upon, and existing European-wide national networks will need to be co-ordinated. In the case of both imaging and 'omics technologies, the creation of disease-specific European Networks/Centres will be proposed. These will establish standards, validate imaging biomarkers and encourage the development of accredited regional centres of excellence.

3.1.3 Patient recruitment

The next challenge to accelerating the delivery of safe, effective medicines to the market is patient recruitment, for which there are two key aspects; speeding up the recruiting process and recruiting the right patients. Solving these issues addresses a further question relating to the ability of Europe to compete with the Far East in clinical research. This was a major topic of discussion in the workshops on drug efficacy, and the key to the retention of a thriving clinical trials environment in Europe was seen to be in the active involvement and collaboration of the patients and patient groups, in the creation of pan-European networks and in the quality of patient and trial data. In this connection, it will be important to develop clinical research capability and capacity in the new member states.

Clinical trials consume a major component of the time for medicine development, on average more than 50% of the total. Some trials are performed in parallel while others are performed sequentially relying on scientific results from previous trials. A clinical trial consists of the approval to start the trial, patient recruitment, treatment duration, and reporting. One of the major components is the patient recruitment phase. Composite benchmarking data show that more than one third of the total time for a trial is spent in the recruitment phase which lasts, on average, one year. Reducing the duration of this phase will have a substantial effect on the time for medicine development and will provide a competitive edge in terms of performing clinical trials.

Strategies will be developed with clinicians and patient associations on how to improve patient recruitment. Consideration should be given to the benefits of advertising for recruitment into clinical trials. A potential approach could be through education of patients about the benefits of participating in research. Patients should not only be informed about the outcome of the clinical research but also be involved in the design of the study. Their involvement is important for developing a more patient-centric approach to treatment and for their participation in an educational process involving patients, carers and researchers to ensure best treatment outcomes. In this respect some initiatives have already been proved to be useful, e.g. participation of patient organizations in study groups to reflect upon trial strategy for therapeutic and diagnostic innovations, and participation of patients at various stages of the clinical trials elaboration process. A system-

atic analysis of patients' participation needs to be performed with the relevant European medical research and patient associations. As the concept of personalised medicine becomes a reality, the understanding and willing participation of patients will become ever more important in analysing the relation between genetics and responsiveness. Their influence will also be felt in promoting research into quality of life measures and their incorporation into clinical trials.

The Innovative Medicines Initiative emphasized from the beginning the need actively to involve patients in the research and development process of new medicines in order to ensure a more patient-centric approach. During discussions at the first efficacy workshop on April 4-5, 2005 it became clear that patients' needs were not being adequately addressed by current practice. An issue that seriously impedes the potential of patients' groups is the precariousness of their funding. Sponsorship by the pharmaceutical industry lays them open to accusations of bias in favour of their founders, and the possibility of core funding by the Innovative Medicines Initiative is a proposal that should be further considered.

The value of continuing to run clinical trials in Europe, despite the higher cost per patient compared with the Far East, will depend on the quality of the trials and the added value created by having first class electronic patient records and biobanks allowing intelligent patient selection and investigation of the basis for response and non-response. Essential to this process will be the creation of pan-European networks of academics, physicians, patients and industry, a pan-European IT infrastructure for clinical trials and pan-European research hubs that will become centres for translational medicine research. These will need to be developed out of existing national networks, encouraging them to adopt common standards and protocols across all the member states.

Causes, clinical manifestation, consequences and treatment of disease and disorders often differs between women, men and children and the possibility of such differences will therefore be taken into account in the conducted research.

3.1.4 Regulatory approvals

Regulatory authorities are the final judge of the risk/benefit ratio for each new application. The perception is that the regulatory authorities are becoming more risk-averse - translating into increasing risk management planning which can include requirements for expanded studies to quantify potential serious adverse events. The reasons for this may include increased public and media scrutiny of pharmaceuticals and regulatory decision-making and a perceived lack of robustness of the post-marketing monitoring processes. In addition, there is an increasing tendency for approval of more restricted indications (with requests for more data for broader indications). This can lead to significant delays in gaining marketing authorisation and delay patient access to innovative medicines that address medical needs. A set of recommendations for reducing the time to market, but ensuring the safety of new medicines, will be developed and discussed with the relevant stakeholders and specially the EMEA in a spirit of co-operation and transparency. A detailed list of topics for discussion will be drawn up within the first months of the project but may include, among others, proposals on how to:

- Improve dialogue with regulators during development prior to regulatory approval to help to reduce requests for additional data and regulatory questions following submission. The so called EMEA Pipeline Project is a welcomed opportunity for Industry to work closer with the EMEA to help expand and improve the range of guidance available in Europe by sharing the Industry view formed through Research and Development experience in different therapeutic fields. In this context, collaboration with other regulatory agencies, for example the FDA, in order to improve consistency across regions and share best practice would add further value.
- Increase the acceptance by regulatory authorities of biomarkers and surrogate clinical end points. New biomarkers have the potential to speed the availability of medicines to patients if they can also be used for regulatory decision-making. They are already used to inform development decisions in Industry and there is a progression and continuum from 'biomarker' (used as a development tool) to 'surrogate end-point' (sufficiently widely accepted to be used as the clinical basis of approval). This should be done on the basis of the new procedure for European Union Guidelines recently published by the EMEA. This Guidance is a clear improvement of the procedure for a transparent development, consultation, finalisation and implementation of new guidance documents in the EU.
- Increase the involvement of other stakeholders such as patients in the regulatory review process. Patients often take a different view from the regulators of the risks that they are prepared to take when weighed against the potential benefits of a new medicine. However to safeguard patients this must go hand in hand with appropriate support, information and surveillance after drug approval.

An important research area will be into the quantification of quality of life measures. The development of ways to measure drug efficacy beyond the usual primary efficacy endpoints is important to prevent potentially valuable drugs falling by the wayside but only if such measures are incorporated into the clinical trials process. Such studies can be used to inform future health economic considerations of new therapies. To promote this, a European Stakeholder Consortium, consisting of patients, regulators, health care providers, industry, physicians, and medical insurance companies will be established. This will address quality of life issues, cost and burden of disease.

- Develop methods to collect data on risks and benefits of medicines once they are available in a real world setting. Evaluation of the long term and real life benefits and risks of medicines after launch should use information from randomised clinical trials and from observational/epidemiological studies that use electronic patient-level data (e.g. data from medical records). It is therefore important that databases containing this information are developed and these resources made available for academic and industry research. Improvement in post marketing surveillance methods should speed up the approval process by providing reassurance that risk/benefit issues will be properly considered and could reverse the current trend to increase the scope and size of clinical trials,
- Develop and ensure appropriate use of early conditional approval for innovative new medicines with an adequate safety profile. Improvements in risk management processes including pharmacovigilance would certainly encourage such approvals. Use of such procedures needs to be balanced encouraging development of innovative medicines where further post-approval work is justified, while avoiding unnecessary application of post-submission conditions to other products, serving only to extend the current trend to limited approvals. Alongside this there is a need to develop new tools for regulatory review (e.g. rolling review) with entry criteria that allow reasonable numbers of products to benefit,
- Develop with the regulators, proposals to increase sharing of data, for example on the placebo arms of clinical trials. There is a huge reservoir of data held in EMEA and national agencies that could be pooled to provide baseline information to guide clinical trial design (for example calculating statistical power) for new treatments. Similarly, the regulatory bodies hold data on the pharmacokinetics of a large number of drugs. Collective analysis of the data for all substrates of a particular metabolising enzyme e.g. cytochrome 2D6 or 3A4, should provide information not only on the inherent functional variability of these enzymes within the patient population, but also allow one to determine quantitatively the contribution of such factors as age, gender, disease, and inhibitors of these enzymes, to the variability. Armed with this generic information, one should be able to predict a priori the likely variability of the pharmacokinetics of a new drug within the patient population, under a variety of situations, thereby facilitating future design of clinical studies and subsequent product labelling, and also improving the cost-efficiency of such studies. This proposal will require not only inter-company collaboration but also the agreement of EMEA and national bodies to release these data (Figure 12).
- Encourage discussion on a more flexible approach to clinical trials that reflects the individual needs of particular disease areas. This would include not only the proposals above about surrogate endpoints, quality of life measures and baseline data, but also rethinking the classic phase I, II and III design and to modify this where opportunities arise to streamline the process. There are arguments that the whole statistical basis of clinical trial design needs reassessment e.g. the investigation of Bayesian approaches, in order to increase the effectiveness of trials and reduce their size and cost.

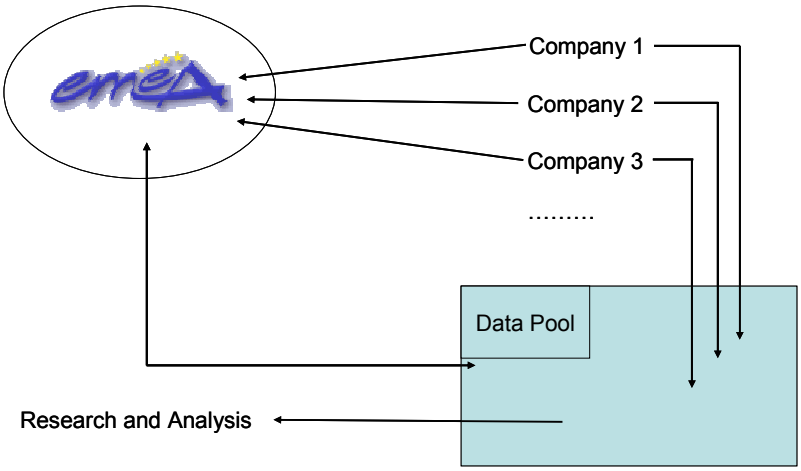

Figure 12: Potential data sharing model

3.1.5 Data sharing

A critical issue for the future success of this initiative will be the willingness of all stakeholders to share pre-competitive data much more freely than before. The advantages to be gained have already been illustrated above by the example of sharing baseline data, however, the issue is not one that can be decided simply between the industry and the regulators. To create the intelligent clinical trial environment so vital to the initiative, it will be necessary to agree on the kinds of data that will be required to build the patient data-bases of the future, to whom the data will be made available, and to understand the IP implications of bio-marker data, as well as the ethical and legal issues around patient consent and confidentiality.

3.2 Cancer

3.2.1 Summary

Over 2 million new cases of cancer will be diagnosed in the EU over the next year. This represents a huge healthcare and financial burden to the member states. The treatment of many cancers is inadequate and represents an important area of unmet need in healthcare provision.

Our rapidly expanding understanding of the molecular pathology of cancer development and progression offers a tremendous opportunity for exploitation of the underlying science into safe and effective new therapies. Approximately 50% of all new chemical entities (NCEs) in development are being aimed at the cancer market, but the development of these NCEs is slow and economically high risk. Although cancer drug development has particular problems such as tumour heterogeneity, the main bottlenecks affecting the rapid delivery of new therapies are similar to other therapeutic areas. The predominant issues centre on the identification and validation of biomarkers, together with development of more relevant pre-clinical disease models that better predict clinical outcome. Specific proposals for each of the main bottlenecks are summarised below:

Identification and validation of biomarkers

- Establishment of a core Cancer Biomarker Network of Excellence with responsibility for the definition of standards and to outline the plan for the Regional Biomarker Centres,
- Creation of Regional Biomarker Centres (4-6 required) to service populations of 50-60 million, handling and processing in the region of 50,000 samples annually, using a broad range in technologies, to defined protocols and standards,
- Development of a Cancer Biomarker database to collect and collate all scientific and clinical data from relevant trials, to underpin the validation process,
- Molecular pathology NoE to underpin the biomarker programme and to develop standards for molecular pathology biomarkers,
- Establishment of a Clinical Imaging NoE to link with ongoing FP6 activities in the area of imaging biomarkers,
- Linkage of Industry, SME's and academic centres for development of translational research programmes through an extended Network of Excellence in Translational Science.

Pre-clinical Pharmacology

- Development of novel predictive in vitro and in vivo models,
- Establishment of Cancer Stem Cell Network of Excellence and research programmes in various cancer types,
- Development of Web based Clinical Pharmacology NoE and research programme for Modelling and Simulation,
- Establishment of Systems Biology Cancer Specific NoE and research programmes focussed on cancer invasion and metastasis and lung diseases.

Patient recruitment and Risk assessment

- Development of a pan-European Cancer Trials Website,
- Creation of European Research Centre for Uncommon Cancers,
- Establishment of a European Stakeholder Consortium to enhance our understanding of Value Demonstration in evaluation of novel anti-cancer therapies,
- Formation of a forum with Regulatory Authorities to discuss issues relating to trial design and regulatory evaluation.

The proposed programme will generate large quantities of data from a variety of sources. Capacity to search, query, extract, integrate and share data in a scientifically consistent manner across these sources

(clinical and scientific datasets) will be challenging, with proposals illustrated in the Knowledge Management section.

The potential for success of this programme will be significantly increased if supported by a strong educational programme, such as described within the Education section. Establishment of a European Medicines Research Academy (EMRA) would support the delivery of a translational, trans-disciplinary educational programme to support all clinical and scientific staff. In addition an educational programme to support patients carers and patient groups would be essential.

3.2.2 Introduction

The treatment of cancer represents a major area of unmet need across Europe and all other areas of the world. Although the aetiology of different cancer varies, all are associated with a loss of cellular growth control. It is a major cause of morbidity and mortality across the world, with over 1.4 million cases in the US figures this year, with a similar incidence across the old EU, with almost 1.5 million cases. In Western Society approximately one of every four deaths is from cancer. Unfortunately, survival rates in Europe for the common cancers remain inferior to US figures with almost 1 million deaths per year (Figure 14). These figures do not include diagnoses of in situ (preinvasive) cancer or the approximately 1 million cases of non-melanomatous skin cancer that will be diagnosed this year.

Cancer	Cases	Crude	ASR (E)	ASR (W)	Deaths	Crude	ASR (E)	ARS (W)
Oral cavity and pharynx	53556	14.29	12.71	9.28	**20178**	5.38	4.64	3.31
Oesophagus	24812	6.62	5.38	3.71	**22917**	6.11	4.85	3.29
Stomach	70798	18.89	14.13	9.35	**54919**	14.65	10.58	6.81
Colon/Rectum	217526	58.04	44.04	29.36	**111781**	29.82	21.38	13.63
Liver	31057	8.29	6.41	4.37	**34132**	9.11	6.81	4.51
Pancreas	41340	11.03	8.35	5.53	**45599**	12.17	9.02	5.88
Larynx	23304	6.22	5.45	3.92	**10326**	2.75	2.28	1.59
Lung	196836	52.52	42.16	29.12	**183653**	49.00	38.27	25.96
Melanoma of skin	38213	10.20	8.89	6.81	**9010**	2.40	1.94	1.37
Breast	210631	56.20	48.84	35.38	**73592**	19.63	15.57	10.61
Cervix uteri	22618	6.03	5.35	4.15	**10098**	2.69	2.17	1.52
Corpus uteri	37411	9.98	8.31	5.81	**8998**	2.40	1.70	1.08
Ovary etc.	34468	9.20	7.74	5.60	**22999**	6.14	4.78	3.23
Prostate	144504	38.55	27.77	17.97	**56035**	14.95	9.73	5.72
Testis	8810	2.35	2.25	2.13	**641**	0.17	0.15	0.13
Bladder	73132	19.51	14.70	9.78	**29773**	7.94	5.44	3.35
Kidney etc.	46228	12.33	10.10	7.21	**22418**	5.98	4.54	3.03
Brain, nervous system	28866	7.70	6.91	5.66	**21681**	5.78	4.97	3.77
Thyroid	16311	4.35	3.99	3.22	**3245**	0.87	0.63	0.41
Non-Hodgkin lymphoma	52440	13.99	11.50	8.46	**25906**	6.91	5.24	3.55
Hodgkin's disease	8407	2.24	2.13	2.01	**2251**	0.60	0.49	0.36
Multiple myeloma	21426	5.72	4.36	2.92	**15259**	4.07	2.93	1.88
Leukaemia	43518	11.61	9.55	7.52	**29714**	7.93	5.97	4.20
All sites but skin	1580096	**421.57**	**338.83**	**238.85**	**929992**	**248.12**	186.54	123.93

Figure 13: Cancer mortality in the EU

Importantly, cancer does not affect all races equally, both in terms of incidence and outcome. From US statistics, African Americans are more likely to die of cancer than people of any other racial or ethnic group. From 1997 through 2001, the average annual death rate for all cancers combined was greatest for African Americans, followed by white Americans, Hispanics, American Indians/Alaska Natives, and Asians/Pacific Islanders. Many countries, including the US (*Healthy People (HP) 2010*) and the UK are aiming to reduce cancer incidence and mortality by altering lifestyle and public health initiatives.

The incidence of cancer varies widely in the EU, both between and within tumour types due to variations in environmental exposure to carcinogens and other reasons. Figure 14 illustrates the incidence and prevalence figures for cancer across the 'old' EU. The incidence and prevalence of different cancers at 5 years varies widely between countries even allowing for the differences in population size. These prevalence figures are an important indication of the overall cancer burden on EU society, which is a function of both the incidence and prevalence of the diseases, with many prolonged systemic treatments. As we are now wit-

nessing significant improvements in cancer outcomes, initially childhood and haematological malignancies, but more importantly recently the common cancers such as breast and colorectal cancer, the cancer 'burden' is significantly increasing in EU populations. Prevalence figures at 5 years indicate over 4 million people affected, with this number likely to increase substantially with the increase in size of the EU and with improvements in treatment.

Population	Cases	1-year prevalence	5-year prevalence
European Union	**1571351**	**1108845**	**4383216**
Austria	32828	23349	93377
Belgium	47575	35107	136267
Denmark	23666	15733	61252
Finland	20473	15068	59867
France	245662	189262	760295
Germany	346558	243658	960318
Greece	36505	24139	95236
Ireland	12461	8025	31216
Italy	264551	190746	750540
Luxembourg	1683	1196	4624
The Netherlands	62647	47170	187560
Portugal	36588	26066	104738
Spain	151046	106444	430202
Sweden	40066	30079	121628
United Kingdom	249042	152804	586096

Figure 14: Incidence and prevalence of cancer across EU countries

The results of cancer treatment have improved dramatically over the past two decades. These improvements have included better organisation of services, greater investment in support services such as X-ray and pathology services, improved screening services enabling earlier diagnoses, in addition to advances in cancer treatments.

3.2.3 Present status of the disease area

The treatment of cancer has improved dramatically over the past 10 years, with improvements now being observed in many tumour types. The initial improvements in survival were initially seen in childhood cancer and haematological malignancies, however we are now seeing significant improvements in many adult solid tumours with early diagnosis vitally important.

Many factors have influenced the recent improvement in survival rates seen with acute cancer treatment. Improvements in health facilities, improvements in organisation of treatment delivery such as the establishment of multidisciplinary care and introduction of screening programmes, together with increased public awareness of cancer have all had an impact. In addition, improvements in surgery, radiotherapy and systemic treatments have also had an impact on outcome:

- Improved quality of local treatment (surgery and radiotherapy) and supportive care, use of effective systemic adjuvant therapies e.g. breast and colorectal cancers,
- Introduction of new chemotherapy drugs,
- Development of novel targeted therapies e.g. growth factors – imatinib, trastuzumab, erlotinib, cetuximab and gefitinib; anti-angiogenesis – bevacizumab.

The challenges for cancer drug discovery are commonly addressed from an organ specific standpoint, with significant differences in pathophysiology between different tumour types. However, there are also generic cancer specific issues, which are peculiar to the malignant phenotype, such as invasion and metastases.

However, despite this, the major problem facing cancer treatment remains the lack of quality systemic treatments. It is interesting to note that at present almost half of the new chemical entities in clinical development are being developed against cancer targets. Many of these projects are high risk, however, as there is a general lack of disease related biomarkers to support early decision making on these products.

Overall, the drug development process in this field remains extremely slow, inefficient and costly. We urgently need to be able to accelerate the process of progressing new potential cancer therapies into the clinic. The blocks to the drug development process in cancer are, in general, similar to other disease areas, with the major problem areas of pre-clinical pharmacology, identification and validation of biomarkers and patient access issues. However, there are specific issues particular to cancer:

- Cancer represents wide range of diseases each with individual biology/issues,
- Inter and intra-tumour heterogeneity is major problem,
- Greater understanding of pathophysiology required for all cancers,
- Improved therapy considered an 'unmet need' for the majority of adult cancers,
- Particularly for common solid tumours,
- Lack of efficacy predominant issue,
- Safety important, but currently secondary issue,
- Drug resistance to targeted therapies,
- Lack of validated biomarkers,
- Inadequate surrogates of long term survival,
- Need for complex biomarkers,
- Mechanistic markers for proof of mechanism less of a problem,
- Lack of appropriate pre-clinical models predictive of efficacy,
- Targeted treatments,
- Biopharmaceuticals,
- Stem cell models.

There remain limitations to how we work in the Cancer community. With several notable exceptions such as the European Organisation for Research and Treatment of Cancer (EORTC), we tend to work in relatively small groups or networks, frequently limited by national boundaries. However, for particular cancers there are very successful tumour specific groups, such as the Breast International Group (BIG). Also as part of Framework 6, a Network of Excellence 'CONTICANET' has been established to co-ordinate the research and treatment of the connective tissue cancers across the EU.

The links between Industry and Academia currently are sporadic and uncoordinated; therefore we have been unable to exploit the potential synergies between them. This results in a slower, more costly and generally over-regulated process. The relationship with between Industry and the regulatory bodies is variable and less successful than in the US. Although the scientific/clinical interface in the cancer field is better than in some other therapeutic areas, there remains an urgent need to develop the translational interface between basic and clinical research. The links with patients, their carers and patient support groups remains at all levels (academia, industry, etc.) and we urgently need to involve these groups more effectively in our scientific and clinical programme designs. Throughout the Oncology community there is an urgent need for education, training and Knowledge Management support for not only the physician/scientist community but also patients and their carers.

The EU has rightly judged that it is important that patients groups are actively involved with the planning and operation of EU Research Programmes. This is strongly supported in the Cancer arena where there are many emerging patient groups. This underpins this proposal.

Cancer research and treatment is functionally "multi-disciplinary" at all levels. This proposal builds on this strength to involve a broad range of health care professionals, of established industrial partners and of SME's. These groups offer a diverse array of skills, the combination of which identifies the EU as a potential leader. This aspect of the programme will strongly link with the training and education packages and will also benefit from developments in Knowledge Capture and Management.

Within the EU, both the major industrial partners and the SME's have a substantial potential for growth. The opportunities are enormous particularly in the cancer field, but developments for cancer would also offer significant 'collateral' benefit to many other therapeutic areas.

The opportunities include but are not limited to the following areas:

- Identification and development of biomarkers,
- Identification and development of diagnostics,
- Imaging hardware and software for digital integration of data.

3.2.4 Bottlenecks

3.2.4.1 Identification and validation of biomarkers

The use of biomarkers in early drug development has been identified as a major route by which we can improve our success rates and improve the efficiency of the drug development process for cancer drugs. Development of validated biomarkers of efficacy and safety could significantly improve our decision making process in early development by:

- Early identification of proof of mechanism and proof of principle,
- Aid in decision making over schedule and dose,
- Identification of sensitive sub-groups for personalised medicine,
- Early identification of unexpected side effects,
- Reduction in risk of late stage attrition.

Biomarkers in the past have focussed on 'simple' or mechanistic biomarkers using standard biochemical and pathological techniques. Increasingly biomarkers are being identified using a variety of evolving platform technologies, including genetics, omics, molecular pathology and imaging, with this raising a number of interesting challenges. Identification, standardisation and validation of these biomarkers are essential prior to them being useful to us in the regulatory process.

These biomarkers can be used for a variety of functions within the drug development process including:

- Diagnostic and prognostic markers for various cancers,
- Predictive markers for efficacy,
- Surrogate 'markers' (end-points) for long-term drug efficacy,
- Predictive tumour genotyping for efficacy (responders/non-responders and safety).

The identification, standardisation and validation of biomarkers would dramatically affect the quality of decision making in cancer drug development and therefore is pivotal to this submission, with a number of core proposals:

- Establishment of a core Biomarker Network of Excellence with responsibility for the definition of standards and to outline the plan for the Regional Biomarker Centre.
    - Development of common European standards for validation of biomarkers,
    - Coordination of national networks, tissue banks, clinical expertise, SMEs and pharmaceutical industry,
    - Regulatory standards and dialogue/ acceptance of validation.
- Creation of Regional Biomarker Centre to act as reference centre for biomarker measurement and to act as the central hub responsible for the 'system of accreditation' of all laboratories performing biomarker assays. This is to ensure common standards, methodologies to service the EU population. The network would be responsible for handling and processing all clinical approved trial samples, using a broad range of technologies, to defined protocols and standards.
    - Genotyping: personalised medicine,
    - Pharmacogenetics,
    - Omics,
    - Novel technologies.

- Development of a Cancer Biomarker database to collect and collate all scientific and clinical data from relevant trials by pulling and pooling information from existing sources, to underpin the biomarker validation process and to facilitate learning across tumour types,
- Integrated research programme using Systems Biological platforms to assist in the identification and prioritisation of potential biomarkers. This would include the use of modelling and simulation of cellular and extra-cellular pathways/networks to select from amongst a variety of options through sensitivity analysis and similar approaches. Other approaches would include analysis of tissues and body fluids to assemble a profile of gene expression, protein and metabolite distribution. Such "triomic signatures" would be associated with specific biological processes, such as metastasis and invasion, supported and validated by appropriate multivariate statistical analysis,
- Development of a pathology Network of Excellence to support the biomarker programme with quality molecular pathology including digital telepathology, to enable pathology QC/review; together with standardisation for molecular pathology biomarkers,
- Development of a Translational Science Network of Excellence to promote standards of translational research and to develop an integrated programme of research.

Establishment of a Clinical Imaging Network of Excellence Programme to link with the pre-clinical EU NoE established via Framework 6. The aim of this group would be to establish imaging standards, approve Imaging Centres in whole body in vivo imaging techniques such as MRI, microPET, microCT and to develop Image analysis/informatics processing solutions. This Network will also be responsible for the identification of imaging biomarkers particularly in the following prioritised areas:

- Angiogenesis,
- Invasion,
- Apoptosis/Proliferation,
- Correlation of pre-clinical imaging with clinical outcome.

These high throughput technologies (*e.g.*, genomics, proteomics, metabolomics) will result in data generation on a massive scale, both in companies and regulatory bodies, on all products, covering R&D across all therapeutic areas. These pre-competitive data can be used to increase the predictive power of current models. The emerging systems biology approach, for instance, requires both data integration at the molecular level (*e.g.*, "omics") and the availability of sophisticated mathematical or computational models at the pathway, cellular, organ or disease physiology levels (so-called multiscale models). Although such modelling efforts are still in their infancy, they are rapidly coming of age and some integrated computational models are already in use. The Knowledge Management work stream as outlined in this SRA is aimed at exploiting the data generated from these proposals to the full and is fundamental to both this and the following sub-section.

3.2.4.2 Predictive pharmacology

There is an urgent need for better and more informative pre-clinical models predictive of clinical outcome. These will be used to facilitate better understanding of disease, identify new targets and predict response to therapy using novel candidate drugs. Major areas for development include:

- Establishment of a Network of Excellence for Predictive pre-Clinical Models.
    - These models will include In-vitro stem cell and engineered cell lines and models of invasion and metastases. Techniques will be developed to purify stem cell populations from common cancers. These could be used to identify novel cancer specific targets, to understand cancer biology and to evaluate the efficacy of established and novel agents against these populations.
- Development of a European web-based Clinical Pharmacology Modelling and Simulation Network of Excellence.
    - Use of in silico modelling and simulation in all stages of drug development,
    - Improved study design to address regulatory questions, minimizing patient numbers whilst protecting safety and ensuring an improved benefit to cost ratio.

- Increased use of Modelling and Simulation will help the understanding of exposure / response relationships with regard to both safety and efficacy. It will help to understand the drug metabolism and also the target biology in humans. Modelling can also be applied in the context of a disease biomarker, helping to understand the variability, signal-to-noise ratio and linkage (causative vs. co-incidental) of a biomarker or a pattern of markers to different disease stages. Clinical trial simulation is a valuable tool to test trial design factors, identifying non-robust co-variates likely to jeopardize trial outcome. The resulting study designs will be more robust, execute faster with less subjects, less non-responders and less adverse effects. The resultant clinical programmes will be cheaper as well providing more informed decisions.

- Systems Biology: Establishment of Cancer Specific Network of Excellence.
  - To develop European expertise in Systems Biology further, with a particular focus on cancer. This will be achieved through building understanding from the Systems Biology programmes established in Framework 6 to capture learning and to share experience. Further, there is a need to collate the wealth of information, knowledge and technologies from Systems Biology approaches that have been used widely to study signal transduction, and to validate the approach in the context of cancer biology. To do this, we would recommend the establishment of a Network of Excellence in Systems Biology. This NoE will facilitate the co-ordination of research between academia and Industry, building on existing relationships with academic centres of excellence active in the field, many of which already focus on aspects of cancer biology, as well as co-coordinating information exchange with other European and nation-specific initiatives in this emerging discipline. The NoE would be responsible for outlining research programmes where Systems Biology approaches would enhance our understanding on disease mechanisms and target function, for example in the field of invasion and metastases, specific to cancer, and/or lung disease, spanning cross-disease interests in cancer, respiratory physiology and inflammation.

3.2.4.3 Patient recruitment: dedicated contact-networks (patients, clinicians, academia, industry)

Patient recruitment is often the time limiting factor for clinical trials. The objective of these proposals is to speed up the recruitment of appropriate patients and to involve patient groups throughout the clinical trial process. Specific proposals are as follows:

- Establishment of a pan-European Cancer Trials Information Website to provide information to the public about the value of cancer trials and treatments. This website will also provide access to existing databases of on-going and planned trials and databases of results,
- Creation of Clinical Network of Excellence (European Research Centre for Uncommon Cancers) focussed on the treatment of uncommon cancers. The aim of this group is identify rare patient populations to facilitate clinical research, to provide information to patients and patient groups about these cancers and to facilitate the development of an integrated translational research programme. This would stimulate the development of novel therapies for commercially non-attractive indications,
- Establishment of a European 'Value Demonstration' Consortium to integrate patient focussed quality of life data, patient reported outcomes and burden of disease,

As outlined in the summary, the Cancer Efficacy proposal will be supported by developments proposed in the Education section. Training programmes for health professionals will address issues of key skills availability and CME. In addition the availability of training programmes for patients and related group, in addition to the establishment of the Clinical Trial Website will significantly improve patient recruitment.

3.2.4.4 Risk activity & outcome assessment with authorities

Adaptive/innovative trial designs for phase I, II & III with phase IV Risk Management activities for Post-Marketing activity:

- Establishment of discussion forum with regulatory authorities, to include representation from patient groups, academia and industry to discuss issues relating to patient access and trial design, to include review of regulations on the use of novel therapies in exploratory clinical research programmes.

3.2.5 Resources

In this section the costs of the recommendations have been estimated and are displayed by project proposal for each bottleneck. The duration of most of the research topics proposed is between 5 and 7 years and all figures are expressed in million euros per year. As many of these proposals are in outline format the costs represent a best guess by the participant group. These figures will be updated as the proposals are developed and approved.

Cancer: Efficacy Summary

Cancer Efficacy	
Recommendations	Costs (mio €)
Identification and Validation of Biomarkers	42.2
Predictive pharmacology	9.8
Patient recruitment and Risk Assessment	14.7
Total (million euros per year)	**66.7**

Cancer: Identification and Validation of Biomarkers

Biomarkers	
Recommendations	Costs (mio €)
Establishment of Biomarker NoE	0.8
Regional Biomarker Centre including biomarker assays and Informatics	20.0
Cancer Biomarker Database	1.5
Integrated Research Programmes Systems Biology	3.0
Pathology Biomarker NoE	2.4
Translational Science NoE and Research Programme	2.5
Clinical Imaging NoE and Research Programme (clinical costs)	12.0
Total (million euros per year)	**42.2**

Cancer: Predictive Pharmacology

Predictive Pharmacology	
Recommendations	Costs (mio €)
Predictive Pharmacology pre-clinical models NoE and Research prg.	2.5
Cancer Stem Cell Programme	5.0
Web based Clin Pharm Mod &Simulation NoE and research programme	1.5
Establishment of Systems Biology (Cancer) NoE	0.8
Total (million euros per year)	**9.8**

Cancer: Patient recruitment and Risk Assessment

Patient recruitment and Risk Assessment	
Recommendations	Costs (mio €)
Pan European Cancer Trials Website	1.5
European Research Centre for Uncommon Cancers and research prg.	4.2
Value demonstration Consortium and validating clinical trial costs	9.0
Total (million euros per year)	14.7

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3.3 Brain Disorders

3.3.1 Summary

In 2004, brain disorders account for a third of all disease burden, and cost Europeans over 135 billion euros in direct health care costs. Current treatments for brain disorders are largely symptomatic and do not respond fully to patient needs. There is an obvious need for disease modifying therapies, and to increase efficacy and tolerability of current symptomatic treatments. The following have been put forward as areas where there is a clear need for further research and where a public private partnership can have a significant impact:

- Identification and validation of pre-symptomatic and surrogate markers for disease progression. Approaches should include genomic, proteomic, and metabonomic profiling in human pathology samples and animal tissues; Functional and structural brain imaging; Correlation of clinical with experimental data and bioinformatics approaches. Establishment of European standards and networks for validation of biomarkers,
- Development of model systems that translate to human pathology and are predictive of clinical efficacy. Use of human material where possible and a better dialogue between clinically relevant and experimental endpoints is needed,
- Better understanding disease mechanisms at systems level. Use of human models of psychopathology and determination of drug effects and dosing using quantitative behavioural and neuroimaging measures,
- Coordination of European stroke networks and development of post injury treatments. Basic research on functional recovery and determination of validated outcome measures for such treatments.

3.3.2 Introduction

Brain disorders account for around 35% of the burden of all disease in Europe[18]. There are an estimated 127 million Europeans living with a brain disorder out of a population of 466 Million and the total annual costs to European society in 2004 have been estimated at €368 billion (€135 billion in direct medical costs, of which €13 billion were directly attributable to drug costs)[19]. Psychiatric disorders excluding dementia disorders accounted for 62% of all costs the remainder accounted for by neurological disorders. The global market for CNS drugs for 12 months to march 2004 was $59.6 billion dollars and is the second fastest growing therapeutic area.[20] Costs of bringing a new drug to market are estimated today at greater than $900 million and the chances of bringing a phase 1 candidate to market in CNS is considerably lower (by up to 3 fold) than other disease areas[21]. Based on incidence costs, burden and an analysis on unmet needs in Europe we have prioritised the brain disorders in the table below.

Neurology	Cases (M) / Costs €bn
Dementia	4.89 / 55.2
Stroke/Trauma	1.83 / 23.8
Migraine	40.78 / 27.0
Epilepsy	2.69 / 15.5

[18] Olesen J. and Leonardi M., The Burden of brain diseases in Europe. Eur. J. Neurol (2003) 10: 471-477.

[19] Andlin-Sobocki P., Jonsson B., Witchen H-U., Olesen J., Costs of disorders of the brain in Europe. Eur. J. Neurol. (2005) 12: supp 1. *In Press*.

[20] IMS Health Retail Drug Monitor March 2004

[21] Kola and Landis, J., Nature Reviews Drug Discovery, (2004) 3, 711-715

Multiple Sclerosis	0.379 / 8.7
Parkinson's	1.158 / 10.7
Psychiatry	
Anxiety	41.41 / 41.4
Affective Disorders	20.87 / 105.6
Addiction	9.194 / 57.2
Psychotic Disorders	3.69 / 35.2

Figure 15: Brain Diseases costs and incidence

3.3.3 Present status of the disease area

For ***Dementia*** some patients receive moderate symptomatic relief with Acetyl Cholinesterase inhibitors (AchEI) or NMDA receptor inhibitors (memantine). There is a clear need for disease modifying agents that could stop or slow the progression of Alzheimer's disease and for more effective symptomatic treatments, including improved efficacy on behavioural symptoms both cognitive and non-cognitive in all dementias. There is a clear need for diagnostic tools for patient selection and for improved surrogates to approved efficacy end points. Because of complex pathophysiology, it is likely that multiple therapies will be required to manage symptoms and control disease in individual patients.

In ***Stroke/Trauma*** Tissue plasminogen activator (TPA) is the only registered treatment for acute stroke, to be initiated only within 3 hours after the onset of symptoms and after a CT scan to exclude haemorrhage. This represents around 3% of stroke patients, with a clear benefit in only 10-15% of treated patients. There is a clear need for treatments that could reduce acute damage or improve recovery post stroke and trauma and for improved clinical access to early diagnosis and treatment.

Multiple sclerosis is currently treated with Interferons (a and b), Copaxon and Mitoxanterone, which have numerous side effects and are considered to be of marginal benefit. The greatest unmet needs are for treatments that halt the progression of the disease.

Epilepsy Several anti epileptic drugs have existed for many years, which control seizures for around 2/3rd of patients, but none are disease modifying and many have serious adverse side effects. Several new antiepileptic drugs (AEDs) have better efficacy and/or better tolerance but disease modifying treatments remain to be found.

Parkinsons's Levo-dopa and dopamine agonists have been used as symptomatic treatments for Parkinson's for more than 30 years but there are still no disease modifying therapies and patients become tolerant to existing symptomatic treatments. The greatest unmet need is for disease modifying treatments.

Affective and bipolar disorders The mainstays of treatment in Europe are SSRIs, with a smaller percentage receiving tricyclics or SNRIs - The next 5-10 years will see an increasingly crowded and genericised market. The need is for improved response and remission rates, reduced mood switching in bipolar patients and a decreased propensity for causing sexual dysfunction. This may be achieved by new classes of drugs now in development and by more personalized prescribing, informed by pharmacogenomics.

Schizophrenia The mainstay of treatment is atypical antipsychotics e.g. risperidone, olanzapine, quetiapine, clozapine. The continuing long term side effect burden - weight gain, metabolic problems and lethargy - as well as efficacy limitations, contributes to compliance problems. New mechanistic approaches are clearly needed as all present therapies are targeted to dopamine D2 receptors to some degree. The level of unmet need is high for positive, negative and cognitive symptoms,

Migraine Acute treatment is necessary for all attacks of migraine. The triptans are effective and well tolerated, but few patients get completely pain free and many have recurrence of attack. About 10-20% of patients who have frequent attacks need prophylactic drug treatment. Only drugs with another primary indication are available, they are generally not very effective and have many side effects. The greatest unmet need is for an effective migraine specific prophylactic medication and for a more effective acute treatment without cardiovascular side effects.

3.3.4 Bottlenecks

Four key priority areas have been identified by our expert group where there is a clear need for further research and where a public private partnership can have a significant impact:

- Identification and validation of pre-symptomatic and surrogate markers for disease progression,
- Development of model systems that translate to human pathology and are predictive of clinical efficacy,
- Better understanding of disease mechanisms (at systems level) leading to better target selection,
- Application and intervention networks for stroke and development of post injury treatments.

3.3.4.1 Identification and validation of pre-symptomatic and surrogate markers for disease progression

Brain disease addressed	Dementia, Stroke, Parkinson, MS
Scientific approach	• Genomic, proteomic, and metabonomic (including lipidomic) profiling in human pathology samples and animal tissues, • Functional and structural brain imaging, • Correlation of clinical with experimental data and bioinformatics approaches.
How it addresses the bottlenecks	Definition of pre-symptomatic cases for treatment = increased efficacy, development of surrogate markers = increased efficacy reduced drug attrition.
Key players, networks and organisations	AddNeuroMed group (FP6), Industry, SME, Academic groups, FENS (Federation of European Neuroscience Societies), Clinicians, HUGO (Human Genome Organisation), HUPO (Human Proteome Organisation), EMBO (European Molecular Biology Organisation), regulators, European Federation of Neurological Societies (EFNS).
Existing infrastructure and infrastructure needs	Tissue banks, Sample and bioinformatics standardisation. Specialist imaging centres with standardised protocols and transferable data management systems.
Feasibility	Feasible but yet un-validated (high risk).
Resource allocation	Based on the AddNeuroMed network for Alzheimer's disease (€15M) we can estimate at least around €60 million over 5 years if extended to 4 other brain disorders.
Metrics of success	Discovery of pre-symptomatic markers for dementia and Parkinson's, diagnostic markers for acute brain injury (in particular stroke), predictive and surrogate markers of functional recovery in acute brain injuries.

3.3.4.2 Development of model systems that translate to human pathology and are predictive of clinical efficacy

Brain disease addressed	All
Scientific approach	• Use of human tissue wherever possible, development of better animal models incorporating human receptors/ disease mechanisms, • Generation of complex in-vitro models that predict efficacy and alignment of these with current discovery platforms, • Generation of target validation technologies using conditional knock-outs/knock-ins in-vertebrates, Extension of target validation systems to simple model organisms (e.g. zebrafish/drosophila) to express mechanisms relevant to humans, • Chemical genetics probes, functional genomics (e.g. RNAi), pathway modelling. Modelling of clinically relevant endpoints in animal models (e.g. behavioural measures for stroke), • Integration with a relevant biomarker strategy such as that described above into model systems, • Integration of pharmacogenomic approaches into animal/in vitro models.
How it addresses the bottlenecks	Better efficacy of preclinical candidates, less attrition due to non-human translation. Better target validation technologies will result in less failure due to lack of human efficacy. Bringing risk forward by integrating biology earlier into the discovery process will reduce failures due to lack of appropriate efficacy.
Key players, networks and organisations	Academia: particularly groups working on modelling disease systems, Clinicians: A better dialogue between basic and clinical scientists is need to identify relevant model end points. Industry, SMEs (e.g. contract research organisations). In-vitro specialist organisations such as ECVAM (European Centre for Validation of Alternative Methods) and IVTIP (In-Vitro Technology Industrial Platform group). FENS (Federation of European Neuroscience Societies).
Existing infrastructure and infrastructure needs	
Feasibility	Feasible but yet unvalidated (high risk)
Resource allocation	6 key areas and 10 diseases @ €2M = €120 million over 5 years.
Metrics of success	Models that would be validated in the clinic and predict clinical efficacy.

3.3.4.3 Better understanding disease mechanisms (at systems level) for improved target selection

Brain disease addressed	Psychiatric disorders, dementia
Scientific approach	Use of human models of psychopathology: e.g. in anxiety/depression, fear potentiated startle (analogous with animal screening models) or emotional processing (human-specific): determine drug effects and dosing using quantitative behavioural and neuroimaging measures. Better mechanistic understanding of mechanisms of cognitive decline in dementia.
How it addresses the bottlenecks	Extend validity of animal screening models to predict efficacy. Fail candidate drugs early in development on basis of functional tests in healthy volunteers or relevant patients. Rank performance of NCEs in human models to fast-track promising candidate drugs to patients.
Key players, networks and organisations	Academia (neuroscientists, psychologists, clinical scientists, neurologists, psychiatrists), Industry, SME.
Existing infrastructure and infrastructure needs	
Feasibility	Very high – but requires pre-competitive development of standard profiles of sensitivity for human tests.
Resource allocation	Core support for network of 10 academic centres per disease area with 3 major disease areas: €2M each (total €60M) over 5 years. Support for a co-ordinating SME: €30M over 5 years
Metrics of success	Investment in specific projects by the pharmaceutical industry: early Phase 1 discrimination of multiple candidate drugs leading to go/no go development decisions

3.3.4.4 Coordination of clinical intervention networks for stroke and development of post injury therapies

Brain disease addressed	Stroke/Trauma
Scientific approach	• Standardisation (by comparison) of methods in European rapid intervention networks for acute treatment of stroke patients. Alignment with national efforts to produce a European standard, • Basic research on medicines to improve functional recovery and determination of validated outcome measures for such treatments, • Basic research into post injury neurobiology including plasticity and neuroregeneration.
How it addresses the bottlenecks	Will allow acute intervention therapies to be improved and reduce attrition. Development of novel approaches based on post injury plasticity and neuroregeneration will generate new therapeutic fields. Development and definition of outcome measures will allow assessment of treatments and thus reduce attrition of post injury therapies
Key players, networks and organisations	Clinical networks (e.g. European Brain Injury Consortium and European Brain Council), academia, rehabilitation professionals and stroke networks, patient groups (e.g. EFNA), industry associations device industry, SMEs, European stem cell networks.
Existing infrastructure and infrastructure needs	
Feasibility	For intervention centres is high for post injury treatments is unknown.
Resource allocation	Coordination of European acute centres will be achieved through specific support actions (€1.25 M). Research into restorative therapies would require €20M for academic groups and around €20M for SME participation in the projects. It is estimated that this would support around 5 strategic research projects (STREPS) over 5 years.
Metrics of success	Novel treatments for brain injured patients, validated measures for post injury recovery. More stroke patients assessed within 3 hours

3.3.5 Resources

Total resources required to implement the current priorities has been estimated at € 311.25 million for a period of 5 years. This is based on the following assumptions; 2-3 large integrated projects for the identification of pre-symptomatic and surrogate markers; 4-5 integrated projects and up to 10 focused strategic projects (STREPS) on the development of more predictive disease models; 3 integrated projects for better understanding of diseases at systems level in psychiatric disorders including dementia; 1 specific support action for coordinating stroke networks and 5 STREPS focused on research into mechanism of post injury recovery following acute brain injuries. As many of these proposals are in outline format the costs represent a best guess by the participant group. These figures will be updated as the proposals are developed and approved.

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3.4 Inflammatory Diseases

3.4.1 Summary

1. Identify specific biomarkers (molecular & imaging) of inflammatory disease progression and surrogates of treatment outcome and safety. Validation of the target, using genomic programmes to follow certain mechanisms, is important, as this relationship is usually unknown.
2. Pharmacogenetic analysis of inflammatory disease groups to subtype responders/non-responders (improved efficacy/safety ratio/predictive adverse effect risk).
3. Increased research into disease mechanisms to provide for true-disease modifying therapeutic opportunities as distinct from simple symptomatic treatment
4. Earlier and more frequent interactions between academia, industry and regulators to understand the new sciences and technologies and development of new and better guidelines
5. Faster and better access to therapeutics with high value outcomes in the EU
6. Develop validated quality of life measures that capture drug efficacy beyond primary endpoints used routinely, which could also be used to inform discussions on patient benefits of potential new therapies
7. Develop better (in vivo; ex-vivo; in silico) disease models. This type of modelling should be based on a mechanistic understanding of the disease process as a function of time and not merely on individual potential target molecules, i.e. systems simulation vs. target simulation. Consequently, there is a need to characterise disease progression, since this may lead to an overall reduction in the number and duration of clinical trials. To date, only a few attempts have been made to explore mechanistic modelling of inflammatory disease progression.

3.4.2 Introduction

Inflammation is the body's protective response to an injury. If this response goes unchecked, however, it can end up doing more harm than good, which is what happens in a variety of inflammatory disorders. These cover a broad spectrum of conditions, including: Rheumatoid & Osteoarthritis, Asthma, Inflammatory bowel disease (Crohn's disease and related conditions), Multiple Sclerosis, Chronic obstructive pulmonary disease (COPD), Allergic rhinitis (hay fever).

Chronic inflammatory diseases represent the greatest collective burden of suffering and economic cost in the developed world:

- One in three people affected,
- Tens of billions of Euros in annual health care costs.

Rapid progress in inflammation science and medicine have led to many new treatments and reduced suffering for millions, but there is much still to be done. Many of the current therapies available today for inflammatory disorders treat only the symptoms of the disease, and not the underlying cause of inflammation. Although inflammation is the unifying factor among the diseases listed above, the treatment approach required for each type of inflammatory disease may be unique.

3.4.3 Present status of the disease area

- Inflammation represents wide range of diseases with individual needs,
- Early diagnosis is important for all inflammatory diseases,
- Lack of true disease modifying treatments is major problem although examples of disease modification are beginning to emerge in RA and some other inflammatory diseases,
- Greater understanding of pathophysiology required:
    - The underpinning science is evolving (innate immunity; adaptive immunity but there is a big gap between immuno inflammatory pathway analysis and true understanding of disease pathophysiology,
    - Translational Inflammation research still nascent,

  - Lack of understanding linking pathophysiology, phenotype, genetic and protein markers to clinical outcomes,
  - Lack of understanding around how specific inflammation responses/defects lead to different disease outcomes in various organ systems. What are the common themes within inflammation and what are the differences which ultimately defines the phenotypes.
- Lack of EFFICACY still key issue.
- SAFETY currently also an important issue.
  - Lack of understanding about how specific immunomodulation leads to various outcomes on efficacy, host defence, some predictable and unpredictable events.
- Lack of validated biomarkers.
  - Inadequate surrogates of long term benefit,
  - Lack of diagnostic, prognostic and safety markers,
  - Need for complex biomarkers and "fingerprints" of efficacy and safety,
  - Mechanistic markers for POM,
  - Lack of standardisation.
- Lack of appropriate and predictive pre-clinical models linking human disease to animal models.

How are we working?

- Multiple relatively small groups/networks,
  - National,
  - Disease specific.
- Industry-academia interface sporadic, uncoordinated,
- Agreed Pan-European Diagnostic/Treatment Disease Definition & Rx standards not available or not applied for most inflammatory diseases,
- Relationship with regulators could be enhanced,
- Regulatory guidelines require updating to reflect medical need and disease outcomes and appropriate endpoints for clinical trials,
- Scientific/clinical interface requires significant improvement, NB focus on translational science (bridging required!!),
- Inadequate interface with patients at all levels (academia, industry, etc.),
- Need for education, physician/scientists/patients/carer's,
- Need Active Patients' involvement in programme design,
- Need active discussion and participation from payers, health care providers and governments about the unmet medical need and what they are willing to pay.

Inflammatory disease areas where there is both an unmet need AND an opportunity

1. Arthritis: Chronic inflammatory components of Osteoarthritis (OA) and Rheumatoid Arthritis (RA):

   Early diagnosis of RA, reverse, modify RA disease process

   Early diagnosis of OA, retardation or inhibition of the development of joint destruction and prevention of OA development
2. Severe Asthma & Chronic Obstructive Pulmonary Disease
3. Allergic Rhinitis
4. Inflammatory Bowel Diseases
5. Chronic Pain

6. Multiple Sclerosis (discussed in chapter Brain Disorders)
7. Atherosclerosis
8. Transplantation
9. Eczema and psoriasis
10. Nephritis
11. Other less common inflammatory diseases (e.g. alveolitis; SLE; Connective Tissue Diseases) Other inflammatory diseases can also benefit from work on the identified high priority inflammatory disease areas above

Arthritis

Arthritis is a chronic inflammatory disease induced when the immune system attacks and begins degrading body joints. The disease is present in all ethnic groups and exists in many forms, most commonly osteoarthritis (OA) and Rheumatoid Arthritis (RA).

Osteoarthritis (OA)

Osteoarthritis (OA) is a progressive, degenerative joint disease and is the most common form of arthritis. It can affect people at any age but occurs most frequently in middle-aged and the elderly. OA is characterized by the breakdown of the joint's cartilage, causing the bones to rub against each other, which results in pain and a loss of movement; symptoms can range from mild to severe. Affected joints can also cause swelling, warmth, creaking and stiffness particularly after periods of inactivity. Osteoarthritis is unlike other forms of arthritis, such as rheumatoid arthritis or systemic lupus, as it does not affect other organs of the body. At present, there are no disease-modifying drugs on the market for OA. Therapy involves the treatment of the symptoms, i.e. pain and swelling in the joints.

The most interesting characteristic of the European epidemiology of OA, even compared to the US, is the relative size of the 45–64 year-old population. This demographic is very large in Europe and, as this generation continues to age, clearly OA will become an increasingly large problem and, therefore, an opportunity for the introduction of new disease-modifying drugs, see Appendix 3 for data on OA.

Rheumatoid Arthritis (RA)

RA is an inflammatory, autoimmune disease that affects the lining of the joints, causing pain, swelling, and reduced mobility for the patient. The main period of onset of RA is between 35 and 55 years of age. The disease therefore imposes enormous societal costs. RA is not as prevalent as more common musculoskeletal diseases such as OA, but because of its highly debilitating nature, RA patients bear a heavy disease burden. Work related disability represents the single largest societal burden associated with RA, surpassing total RA treatment costs. Recent prevalence studies and a general aging of the population in developed countries have increased understanding of the disease burden associated with RA. In addition to causing significant morbidity and economic burdens, an increasing number of patient based studies have shown that RA leads to premature mortality, which is associated with both rheumatoid complications and an increase in non-specific causes of death, such as infections. The exact mechanism of RA disease pathogenesis is not yet known. However, RA is strongly associated with genetic predisposition. RA therapy as a whole is still some way from reaching an efficacy ceiling, see Appendix 3 for data on RA.

Asthma

Asthma is a common chronic disorder of the airways, characterized by airway inflammation, airway hyper responsiveness, and airway narrowing; it is reversible, with treatment or spontaneously. The annual cost of asthma is estimated to be $16.1 billion in the US and $16.3 billion in the EU (NHLBI, 2004; ERS, 2004), see Appendix 3 for data on asthma.

A survey of asthma severity in Europe (Rabe *et al.*, 2000) found that 18% of asthma patients had severe persistent, 19% moderate persistent, 19% mild persistent and 44% intermittent asthma. Severe asthma is a term that encompasses patients with steroid-resistant, irreversible, refractory, brittle, near fatal and poorly controlled asthma. Although some asthmatics have been severely affected for most of their lives, there appears to be a second group of mainly female, non-atopic adults that develop severe disease in adulthood (ENFUMOSA, 2003).

Asthma is a disease with a moderate to high level of unmet need; the high prevalence, extraordinary economic burden to society, and significant rate of hospitalization are balanced somewhat by the availability of effective treatments, that when used properly, are generally successful at controlling the disease. Despite the availability of successful treatments, there is considerable demand for more effective, more convenient drugs. Combined with the high patient population of this chronic disease, the R&D unmet need in asthma creates significant opportunity for advancing more efficacious treatments.

"The greatest need right now is for a disease-modifying drug. We need to be able to down-regulate the inflammatory response, and slow or stop the progression of the disease. This is likely a number of years down the road." – Disease opinion leader

"The greatest unmet need is in the moderate to severe patient category. We also do not have any drugs that essentially cure the disease, that reverse airway remodelling and that fix airway hyper reactivity." – Disease opinion leader

Chronic Obstructive Pulmonary Disease (COPD)

The term chronic obstructive pulmonary disease (COPD) covers a complex group of disorders characterized by a progressive development of airflow limitation and is set to become the third leading cause of death in the developed world by 2020 (Murray *et al*., 1997). In 2002, COPD was the fourth leading cause of death in the US, with annual costs estimated to be $37.2 billion—double that for asthma (NHLBI, 2004), see Appendix 3 for data on COPD.

Although COPD and asthma are both chronic obstructive diseases of the lung, they differ markedly in the underlying disease process. Consequently, although the majority of drugs used to treat asthma and COPD are the same, they do not provide equivalent benefit in both diseases. Currently, smoking cessation is the only known means of halting the lung destruction associated with COPD, although cessation does not reverse the lung destruction. Meanwhile, only half of moderate and severe COPD patients reach the desired outcome of symptomatic relief and an improved quality of life, largely due to the lack of truly efficacious drugs, which is the key factor preventing patients from reaching the desired outcomes.

"There are no effective drugs for the loss of airway function. We need a drug that improves the quality of life, or survival. Anything that decreases exacerbations will be welcomed." – Disease opinion leader

"I think that the biggest need is to reverse the downhill trend of chronic pulmonary insufficiency. Also, we haven't identified, or haven't had success with, the ability to treat the inflammatory process." – Disease opinion leader

"I think the biggest issue in COPD is loss of lung architecture, and most of the anti-inflammatory approaches in COPD don't work very well. So, I think there's an unmet need to grow back normal lung, especially alveoli. So, if someone could find appropriate growth factors that could restore lung architecture, then that would be a big breakthrough for that disease." – Disease opinion leader

"There are no effective drugs for the loss of airway function. We need a drug that improves the quality of life, or survival. Anything that decreases exacerbations will be welcomed." –Disease opinion leader

Allergic Rhinitis

Allergic rhinitis is by far the most prevalent respiratory condition in the global market, with approximately 146 million suffers. The close relationship between asthma and allergic rhinitis has led to the "one airway, one disease" concept, which regards both diseases as a continuum of inflammation involving one common airway, rather than as distinct entities. According to the WHO initiative on allergic rhinitis and asthma, 10–20% of adolescents and 25–33% of adults are affected by allergic rhinitis. However, rates may differ due to variations in disease definition, diagnosis criteria and type of population studied, see Appendix 3 for data on allergic rhinitis.

IBD [Crohn's Disease (CD) & Ulcerative Colitis (UC)]

CD is a chronic inflammation of the intestinal wall, typically affecting the full thickness of the intestinal wall. Most commonly, it occurs in the lowest portion of the small intestine (ileum) and the large intestine, but it can occur in any part of the digestive tract from the mouth to the anus and the skin around the anus.

In recent decades, CD has become more common both in western and developing countries. It occurs roughly equally in both sexes, and is more common among Jewish people. Most cases begin before the age of 30; the majority start between the ages of 14 and 24. The causes of CD are unknown.

UC is a chronic disease in which the large intestine becomes inflamed and ulcerated, leading to episodes of bloody diarrhoea, abdominal cramps, and fever. The disease can start at any age, but usually begins between the ages of 15 and 30. About 10% of patients who appear to have UC only suffer a single attack. However, a proportion of such patients may actually be suffering from an undetected infection, rather than true UC. For most patients, UC is a chronic disease that waxes and wanes over time. The causes of UC remain unknown. See Appendix 3 for Epidemiology of the IBD population.

Physicians have ranked the lack of therapies for severe disease as an important unmet need in IBD. IBD drug R&D is still some way from reaching an efficacy ceiling.

Chronic Pain

In general, the management of inflammatory and neuropathic pain using currently available drugs is still unsatisfactory, and many people obtain only partial and temporary relief while experiencing problems with side effects. The pathophysiology of chronic pain is poorly understood. Chronic pain may be a result of persistent inflammation at the level of the first order nociceptive neuron; plastic changes at the level of the dorsal horn neuron, thalamus, cortex or subcortical structures; or a combination of persistence inflammation and plastic changes. Although much research has been done to understand the pathophysiology of pain, neuronal mechanisms and pain pathways sub serving pain, much is still unknown. The promise of genomics and proteomics and other related technologies to enhance our understanding of the molecular-genetic basis of nociception, inflammation and plasticity in the nervous system will likely lead to new targets for analgesia in chronic inflammatory diseases such as RA and OA and new chemical entities entering the drug development pipeline. The scientific challenge is to use existing and emerging expertise and technologies to:

- Identify which signals initiate plasticity and develop markers for these
- Discover the participation of novel genes in plasticity that are relevant to pain mechanisms
- Use imaging techniques to identify pain-activated areas in humans that may provide opportunities to follow effectiveness of new therapeutic approaches
- Utilise this information to improve the diagnosis and initiate novel treatment strategies for pain

Understanding of analgesic mechanisms provides an opportunity to move forward to a new way of assessing analgesic for pain based on an understanding of the mechanisms involved rather than the empirical way that has driven analgesic development in the past. The way to move forward clinically is to measure multiple signs and symptoms, not just global measures, to look at the natural history, to validate mechanistic hypotheses, and to gain insight into the mechanisms that operates in the individual patient. There needs to be recognition that laboratory pain models should not only be diseases models but also mechanism models and that these models can be used to screen for novel targets and validate mechanisms using drugs and functional genomic approaches. One of the big challenges is to understand the mechanisms that convert a short lasting pain into a pain that persists and becomes intractable rather than returning to baseline. How can treatments that prevent the development of long-lasting pain be effectively evaluated? Can patients be targeted more effectively by not treating the disease, but the actual mechanism that produces the pain?

The extrapolation from preclinical promise to validation of new therapeutic strategies in humans, however, is costly, time-consuming, and uncertain, representing significant challenges to analgesic drug development and regulatory oversight for safety and efficacy. Therefore, data that can be generated in disease models to help elucidate the mechanism of action for an unprecedented analgesic can supplement required clinical efficacy studies to increase confidence in rationale in the regulatory submissions. There is a critical need to combine preclinical pain models with information generated by anatomy and histochemistry to investigate the contribution of a receptor or channel on the animal's behaviour. These animal models allow prediction of the mechanism of novel drugs in a pain state. However, they do not necessarily predict the response of a human to a particular drug. If a single model is insufficient, observation of similar relative activity across several models provides convergent validation of the pharmacology of that drug's effect. If a drug does not show similar outcomes across models, it suggests that tissue injury models have their own distinct pharmacology. One model may be an effective screening tool that detects the activity of many drugs while other models in which the same agonist does not work may represent models of hyperpathia. Convergent validity suggests that a prediction may play out over a variety of mechanisms.

Building on past research there is a critical need to integrate the wealth of knowledge around various precedent mechanisms of action of analgesics; understanding the effects of NCEs on locally-released mediators of inflammation using in vivo microdialysis; understanding the effects of NCEs on first order nocicep-

tive neurons (IAdelta and C-fibres) using evoked potentials; understanding the pharmacodynamics of BOLD fMRI signals in key brain regions known to sub serve pain signaling in response to induced pain; understanding pharmacodynamic changes in putative nociceptive neuromodulators using magnetic resonance spectroscopy (MRS) and LC-MS of appropriate biofluids; and finally integrating all of the data to provide a reasonable mechanism of action should facilitate registration of unprecedented NCEs.

There is a major need for mechanism and outcome pain biomarkers to:

- Provide objective measurements of pain
- Probe mechanisms of pain in man
- Translate from animal to human biomarkers and to back-translate from patients to man to animals
- Provide objective data to allow early go/no go decisions on NCEs, particularly for unprecedented approaches
- Provide information to help dose-set in Phase 2 studies

Pain biomarkers need to be reproducible, robust and sensitive to clinical pain (disease effects) and to drug (pharmacological) effects, and to behave in a manner that is sufficiently understood that confident predictions can be made when they are employed in drug development studies.

3.4.4 Bottlenecks

The main issues considered by the working group were the following:

- Active patients' involvement - a must-have in programme design,
- Early diagnosis is important for all inflammatory diseases,
- Some of the diseases are increasing in incidence and prevalence and some like COPD are becoming the fastest growing common causes of death, morbidity and health care burden to society,
- Some common pathways understanding of the biology e.g. from smoking could help the understanding of the pathophysiology of COPD, Lung Cancer, Atherosclerosis, Alzheimer's etc.,
- Other inflammatory diseases can also benefit from work on the identified high priority inflammatory disease areas,
- Few disease modifying treatments are available in these indications – critical gap,
- The underpinning science is evolving (macrophages, B cells, T cells, target tissues, genetics, proteomics etc…) but there is a big gap between inflammatory pathway analysis and true understanding of disease pathophysiology.

1. Patients

Given that the EU has judged that it is important that the "patients groups" be involved with the planning and operation of the research, it is an advantage that many inflammatory diseases influence "quality-of-life" and mortality, but still leave the subjects with significant morbidity and enormous health care burden in an aging population.

2. Professional Groups

The work proposal is itself "multi-disciplinary", and the overall proposal involves a unique combination of professionals (Academics, Clinicians), of Established Industries (Pharmaceuticals, Diagnostics, Scanning), of SME's (Biotechnology, Diagnostics, Special support services). Furthermore, each of those groups also includes a diverse array of talents. Thus, each project which is funded by the EU must involve a team, the individual members of which will have to teach their skills to the other members.

3. Industrial Growth

Both the "Established Industries" and the "SME's" mentioned above already have a substantial potential for growth based on existing knowledge. However, the opportunities for the development of new areas are enormous, especially for SME's.

These include, amongst many others:

- Biomarkers,

- Diagnostics,
- Therapeutics,
- Population screening,
- Education,
- Nanotechnology,
- Imaging Hardware Optimised for Measurements,
- Software for Image Quantitation.

The rank order of importance of the bottlenecks is:

- Patient recruitment,
- Identification and validation of biomarkers,
- Predictive pharmacology,
- Risk assessment.

3.4.4.1 Patient recruitment (European asset): dedicated contact-networks (patients, clinicians, academia, industry)

- Patient recruitment is often the time limiting factor for clinical trials,
- A pan-European database of patients with inflammatory diseases with defined uniform diagnostic and patient history data (including prior drug exposure; HLA background, responder/non-responders; disease progression; effects of intervention),
- A pan-European IT infrastructure for clinical trial data management is technically within reach. If standards are established and adopted, this could eventually lead to large reductions in overhead costs for industry and wider possibilities for academics to study healthcare intervention in a pan-European collaboration. This would improve the competitive position of Europe versus the US and Japan considerably,
- A pan-European database will further research into inflammatory disease sub-groups aiding disease profiling,
- Identify & leverage evidence based treatment benefits across different inflammatory diseases and ensure rapid deployment across Europe of such therapies,
- A pan-European information campaign should inform the public about the safety of trials and the importance of participating for the benefit of health care,
- By also identifying academic research centres this would also enable translational research activities allowing a greater understanding of disease sub-groups, heterogeneity, and disease progression,
- Creation of Pan-European Research Hubs in different inflammatory disease areas that capture basic research, biomarker, clinical investigation techniques collectively building on already national initiatives (as is MS in Denmark),
- Need to have an education and training component for clinicians with protected time for research and trial work.

3.4.4.2 Identification and validation of biomarkers

Increasingly, information derived from clinical studies in the ‘field’ of biomarkers and pharmacogenetics is becoming employed in early development. The usage of both this information and data generated in early discovery will provide enhanced predictive capability of compounds’ likely behaviour in man. This enables weak compounds to be failed earlier in development more efficiently, thereby reducing the resource burden associated with high rates of late clinical stage attrition and freeing pipeline resources. Importantly, the usage of clinical information in discovery will promote increased dialogue and collaboration between clinical and academic scientists and those at the laboratory bench. Consequently, the industry can expect the new

drug discovery paradigm to be based on the integration of fields, such as genomics and proteomics, structural biology, chemistry, physiology, pharmacology and population biology, alongside the integration of the clinic and the laboratory.

The big areas for research are:

- Diagnostic & prognostic markers for inflammation & tissue damage,
- Surrogate markers for drug efficacy and safety,
- Markers of host-defence and risk-benefit evaluation etc.,
- Markers for functional recovery or disease modification,
- Predictive genotyping (N.B. Societal implications),
- Population screening not only through genetics but also other technologies that can provide a high degree of specificity and sensitivity,
- **Pharmacogenetic** markers of inflammatory disease groups to subtype responders/non-responders (improved efficacy/safety ratio/predictive adverse effect risk),
- **Pharmacogenetics** (patients, ex: allotype responses to antibodies) 5 years,
- **Polyomics**,
    - Some of the emerging omics technologies will be useful in this area of identifying common pathways between apparently different diseases although in this case it will be important to establish primary etiological changes from secondary effector mechanisms. A further utility for both genetics and other omics will be the evaluation of the comparability of the animal models to human disease. They may additionally be useful in explaining the variation in response that is sometimes observed when compounds are tested against multiple animal models.
- **Pharmacogenomics** (diseases) 20 years,
    - Increased target confidence in mechanisms for inflammation indications with positive human association,
    - The identification of common factors that increase risk or protect against multiple diseases suggests some common physiology e.g. the protective effect of the Delta 32 CCR5 mutation confers protection against both rheumatoid arthritis and ischaemic heart disease. One of the key advantages of using genetics to identify these links is that a temporal relationship between the factor understudy and the indication is established as germ line genetic variation is essentially fixed at conception.
- Imaging: Monitor Disease progression (MRI), the big areas for research are:
    - Bioimaging Centres of excellence for Inflammatory Disease Groups: Will support the drug discovery/development process using whole body in vivo imaging techniques such as MRI, microPET, microCT and High Resolution Ultrasound. In addition to in vivo imaging capabilities the COE can provide PET radiotracer development and image analysis/processing solutions necessary for image quantification,
    - Linkage of Imaging to Monitoring Disease activity & progression,
    - Standardization of BioImaging modalities“,
    - As is building on Cambridge COE for OA.

Validation of biomarkers & and standardization of biomarker assays

The big areas for research are:

- Establishment of European standards for validation of markers,
- Coordination of national networks, tissue banks, clinical expertise, SME’s discovery and Pharma,
- Regulatory standards and dialogue/ acceptance of validation.

3.4.4.3 Predictive pharmacology

The big areas for research are:

- Development of models (in-vivo/in-vitro) that translate to human pathology and are predictive of clinical efficacy and safety and host-defence,
- Tools for functional pharmacology in humans,
- Access to appropriate diagnostic imaging and technology (+ technologists),
- Training of clinical and basic pharmacologists,
- Proof of concept networks (academic networks),
- Systems approach to understanding diseases processes,
- Modelling and simulation in inflammatory drug development.
    - In silico modelling and simulation can be applied at every stage of the drug development process, from the virtual modelling of cellular function, e.g. the whole network of molecular interactions involved in cell biology, to modelling virtual populations. These methods are considered the most likely source of the power and tools required for the much-needed re-organisation of drug development, providing the following:
        - A framework for the continuous integration of drug development knowledge through a European web-based network,
        - Improved study designs and more informative studies,
        - Easier answers to regulatory questions, possibly eliminating the need for more clinical studies and ensuring an improved benefit to cost ratio.
    - For this to happen, it will be necessary to:
        - Encourage the development and application of modelling and simulation,
        - Enhance the confidence of various partners in using models and their outcome,
        - Create models that are as mechanistically-based as possible.
            - Utilise recent advances in molecular modelling, high performance computing technology, structural chemistry and PK/PD and disease modelling to develop new maps predicting molecular events to individual clinical and population outcomes,
            - Develop new technology platforms such as nano-technology as systems integrators to study disease and develop new treatments with high value outcomes.
    - The following partners are equally important in achieving this goal:
        - Academic partners: to develop the theoretical and conceptual basis for the model and perform quality assessment and control of components,
        - Big pharmaceutical companies: to conduct retrospective and prospective analyses of the application,
        - SMEs: to provide specific information (IT, genomic etc),
        - Regulators: to conduct retrospective analyses of the application and establish good practice, i.e. by providing anonymous data for the validation of models by academia and industry and promoting confidence in modelling.

Systems Modelling - Disease Classification to aid Clinical Disease Profile and Indications Discovery

Co-morbidities although expressing different symptomatic phenotypes are likely to provide evidence for uniting molecular pathologies, such as the recognition of obesity, diabetes and hypertension as symptoms of metabolic syndrome. For example for 50 years its have been known that patients with rheumatoid arthritis are far more likely to develop cardiovascular problems due to arterial disease yet only in the past couple of years have we began to investigating and identifying common underlying mechanisms between the two conditions. Mathematical and textual meta-analyses of the existing (published and proprietary) data can be employed uncover co-morbidities. A second phase of dedicated investments in collaborative research work with academic epidemiologists could also be considered.

3.4.4.4 Risk activity & outcome assessment with authorities

The big areas for research are:

- Adaptive/innovative trial designs for phase I, II & III,
- Bayesian methodology and other statistical techniques (e.g. N of 1 trials) to get early readout on efficacy and safety,
- Multidimensional scaling techniques,
- Develop/Amend/Apply validated QoL & Disease Activity & Severity measures that capture drug efficacy beyond primary endpoints used routinely, & which could also predict patient benefits of potential new therapies,
- Establishment of good working practices with authorities early in the process,
- Electronic patient records and electronic data capture technologies.

3.4.5 Resources

Costs of many but not the entire individual inflammation efficacy enablers have been estimated and are summarized in appendix 4. The duration of most of the research topics proposed is between 5 and 7 years. The total cost of undertaking the enablers listed will exceed € 300 million over a period of 5 years. As many of these proposals are in outline format the costs represent a best guess by the participant group. These figures will be updated as the proposals are developed and approved.

3.4.6 List of contributors

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3.5 Diabetes mellitus

3.5.1 Summary

In this paragraph an expert group representing key stakeholders makes a proposal for pre-competitive research in Europe to address the bottlenecks of developing novel therapies for diabetes. This disease was chosen as one research area, since diabetes is an epidemic with a prevalence expanding in an exponential manner. The disease and its complications cause not only human suffering, but it is also a major economic burden for society.

The group has identified 5 major research priorities. These are to a) Develop more predictable preclinical models (in vitro, in vivo, in silico) for diabetes and its complications, b) Identify and validate novel targets in diabetes by discovery research in the pathophysiology of the disease and its complications, c) Identify and validate biomarkers for beta cell function and loss, for insulin resistance and for diabetic complications, d) Characterize subpopulations and patient groups using genomics and biomarkers for focused therapeutic and preventive studies, and e) Develop Quality of live and patient reported outcome metrics to measure impact of novel treatments on daily activities and the overall benefits of novel therapy.

The objective is to involve all key stakeholders, such as pharmaceutical industry, academic centres, patients, regulators, major associations and European Community in this effort in a collaborative fashion.

3.5.2 Introduction

The objective of this chapter is to make proposals for research efforts in order to develop better medications for diabetes and its complications. A multidisciplinary group representing major stakeholders and wide area of expertise was set up to review the bottlenecks in developing novel therapies for diabetes and to make proposals how to address those in a precompetitive manner. In addition, a number of scientists focusing on diabetes research or drug development were consulted for further opinions and ideas.

The major research areas to cover with regard to the prevention and treatment of diabetes and its complications are glucose metabolism, lipid metabolism, obesity and cardiovascular diseases. Since there are other programs focusing on dyslipidemia & atherosclerosis and obesity, the focus of this proposal is research for the normalization of glucose metabolism. Some academic networks already exist in Europe for diabetes projects funded by FP5 and 6. There is no specific budget from the European Commission for diabetes research but “diabetes” is included in the FP5 and FP6.

FP5: 22 projects in most parts of Quality of Life Programme as diabetes must be studied from different angles (EU contribution: € 42 million)

FP6 so far:

First call

- DIABESITY (IP) project: € 11,7 million € - Drug targets for obesity/TP2D,
- TONECA (CA): € 1 million € - Molecular mechanism of beta cell death,
- IMMIDIAB (SSA): € 200’000 – type 2 diabetes in immigrant populations in Europe.

Other related project funded by the EU

EUROTHYMAIDE (IP): major biological functions of the thymus, with emphasis on auto-immune cell destruction (€ 12 million).

Second call

- EXGENESIS (IP): € 12,5 million € - Effect of physical activity on human health,
- EUGENE2 (NoE) project: € 8 million € - Drug targets for obesity/TP2D

Other related projects funded by the EU

- BETACELLTHERAPY (IP): € 11,778 million € - Beta cell programming for treatment of diabetes,
- MOLPAGE (IP): Bio-markers for early diagnosis /identification of people at risk of diabetes and CVD (€ 12 million).

There are three more projects under negotiation from the third call of FP6.

A major issue in development of anti-diabetics is the lack of detailed knowledge on diabetes pathogenesis and related biomarkers in the beta cell, liver and peripheral tissues. Therefore a significant part of this project is related to discovery research to support the identification and validation of novel targets.

3.5.3 Present status of the disease area

Diabetes is an epidemic disease with a current global prevalence of 150 million affected individuals; this prevalence is rising exponentially in concert with an increase in obesity and decrease in physical activity. After 10 years the prevalence of diabetes is estimated to be 250 million. A majority (90%) of patients have type 2 diabetes characterized by abnormal insulin secretion and insulin resistance. The remaining 10% have type 1 diabetes as a consequence of beta cell loss and near total insulin lack. A recent trend is an increase in type 2 diabetes associated with increasing obesity in young age groups, again probably due to the change in the life style. There is also a progressive increase in the prevalence of type 1 diabetes in Europe, but the causes for this increase remain unknown.

There is a huge unmet need and lot of opportunities to improve diabetes therapy. With current therapy a majority of diabetic patients will develop microvascular complications (neuropathy, nephropathy, retinopathy). A life-threatening burden particularly in type 2 diabetes is associated diseases, such as dyslipidemia, atherosclerosis and other features of metabolic syndrome leading to problems such as stroke and myocardial infarction. Currently available therapies are not effective enough to normalize glucose and lipid metabolism and prevent complications. Although a lot of efforts have been made at national level in various European countries to better organize diabetes, no significant improvement in glycemic control at the national level has been achieved in Europe or USA during the last 1-2 decades.

The costs of diabetes are high both regarding the human suffering and the economic burden for the community. In European countries diabetes-related direct costs (diagnosis, treatment, care) are estimated to be on the average 5% of the total health care expenditure. Indirect costs, such as lost productivity due to disability or premature death are about equal to the direct costs.

3.5.4 Bottlenecks

The bottlenecks of drug development for diabetes were prioritized as follows:

1. Predictive Pharmacology

   1.1.Cell based and animal models for type 1 and type 2 diabetes

   1.2. Basic research in the pathophysiology of diabetes and micro- and macrovascular complications

   1.3.Modification of behaviour and life style
2. Identification of biomarkers for beta cell function, mass and for insulin resistance
3. Validation of the biomarkers in vivo and in humans
4. Characterization of focused patient groups for clinical trials
5. Quality of life

3.5.4.1 Predictive pharmacology

3.5.4.1.1 Cell based and animal models for beta cell failure and insulin resistance

Scientific approach	a. **Cell based models**. Identification of novel markers from high risk individuals (beta cell) or markers of insulin resistance in liver, muscle and fat cells (cytokines, adipokines, compounds from NMR analysis etc.) to be introduced and tested in cell models. b. **Animal models** have two steps; first to establish a public database with detailed information on existing models. Second, to develop novel, "humanized" target specific models such as beta cell dysfunction and loss, insulin resistance in the liver, muscle or fat cell, micro- or macrovascular vascular complications, and animal models for human islet transplantation.
How it addresses the bottlenecks	Helps to identify novel pathways and targets, improves the compound predictability and reduces the attrition rate in the drug development. Allows prove of concept to be tested in preclinical and early clinical development, reduces the attrition rate throughout the development phase and the scope and cost of clinical trials
Key players	Academic groups and industry. TONECA network, www.toneca.com, EURADIA, www.euradia.org, EURODIA, academic centres, industry
Infrastructure needs	
Feasibility	Cell based models are feasible, common database for existing animal models is easy, to establish target specific models is difficult
Resource allocation	€ 44 million
Metrics of success	Validation with the in vivo models and with human studies
Generic issues	
Interaction w/ SRA	Knowledge Management

3.5.4.1.2 Basic research in the pathophysiology of diabetes and micro- and macrovascular complications

3.5.4.1.2.1 Beta cell dysfunction and loss

Scientific approach	Molecular signature of functional vs. dysfunctional beta cell using genomics and bioinformatics; this information should be available in open access gene and protein banks. Examine central regulation of beta cell function, and lipo- and glucotoxicity leading to beta cell damage. Use available human samples (plasma, tissues) for novel assays, and available data and bioinformatics tools for in silico research to find out predictive biomarkers and factors associated with beta cell dysfunction and loss. Establish a European Central facility to coordinate isolation and sharing of human islets. Facilitate research to develop beta cells from adult stem cells.
How it addresses the bottlenecks	Novel therapeutic targets, more focused groups for clinical research, bring genomics to the field, allowing maximizing of information from each experimental model
Key players	Beta Cell Gene Exp. Bank (http:tldbase.org/cgi-bin/enter_bcgb.cgi), EURODIA, EURADIA, Eugene2 network, www.eugene2.com, UKPDS database, Botnia database, academy, industry, regulatory
Infrastructure needs	European centre for human islets and a centre for study coordination
Feasibility	Doable
Resource allocation	€ 26 million
Metrics of success	Novel, drugable targets
Generic issues	
Interaction w/ SRA	Knowledge Management

3.5.4.1.2.2 Insulin resistance

Scientific approach	Examine molecular mechanisms of inflammation, oxidative stress, endoplasmatic reticulum stress, endothelial function and their interaction in insulin resistance. Create an open access database of gene expression data in insulin responsive tissues as well as accessible tissues that are regulated by insulin, insulin resistance and diabetes. Use available human samples (plasma, tissues) for novel assays, and available data and novel bioinformatics tools to find out predictors and factors associated with insulin resistance.
How it addresses the bottlenecks	Novel targets
Key players	UKPDS database, Botnia database, Diabetes genome Anatomy Project, USA, www.diabetesgenome.org/home/index/.jsp, Diabesity, www.eurodiabesity.org, Exgenesis, www.dundee.ac.uk/press releases, academy, industry, SMEs, regulators.
Infrastructure needs	Gene databanks, patient databanks
Feasibility	Doable, extensive
Resource allocation	€ 21 million
Metrics of success	Novel targets

Generic issues	
Interaction w/ SRA	Knowledge Management

3.5.4.1.2.3 Microvascular complications (retino-, neuro- and nephropathy)

Scientific approach	Establish target specific animal models and biomarkers. Examine the contribution of hyperglycemia through different pathways (advanced glycated end products, polyol pathway, protein kinace C, oxidation by free radicals etc), genetic background and other factors in the pathophysiology of complications. To find associations and causal relationship use existing human data basis and bioinformatics for in silico research, and blood and tissues samples for novel assays
How it addresses the bottlenecks	Provides novel targets and biomarkers. Brings the possibility to reduce the size and duration of clinical trials.
Key players	Industry, academy, patient organizations, data bases from large studies (EURODIAB, UKPDS etc), regulators.
Infrastructure needs	Gene databanks, Patient databanks, biomarker centre
Feasibility	Doable, extensive
Resource allocation	€ 14 million
Metrics of success	Validated animal model, novel validated targets, successful proof of concept studies in focused patient groups
Generic issues	
Interaction w/ SRA	Knowledge Management

3.5.4.1.3 Macrovascular complications (atherosclerosis, stroke)

Scientific approach	Establish target specific animal models and biomarkers. Use available data and bioinformatics tools as well as novel assays to analyze stored samples from long-term studies to find out associated factors and their potential causal relationship with macrovascular complications. Utilize novel imaging technologies and biomarkers in prospective studies
How it addresses the bottlenecks	Provides novel targets and a possibility to reduce the size and duration of clinical studies.
Key players	Industry, academia, data bases and stored samples from large studies (UKPDS etc), regulators
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre
Feasibility	Doable
Resource allocation	€ 14 million
Metrics of success	Validated animal models and biomarkers. Novel targets. Successful short and small proof of concept studies.
Generic issues	
Interaction w/ SRA	Knowledge Management

3.5.4.1.4 Modification of behaviour and life style

Scientific approach	Develop means to intervene on eating and exercise habits. Find biomarkers and genomic information for responding populations
How it addresses the bottlenecks	Biomarkers, patient recruitment
Key players	Patient groups, industry, regulators, academia
Infrastructure needs	Patient databases, bioinformatics centre
Feasibility	Difficult
Resource allocation	€ 16 million
Metrics of success	Validation of biomarkers, successful proof of concept studies.
Generic issues	
Interaction w/ SRA	Knowledge Management.

3.5.4.2 Identification of biomarkers for beta cell function, mass and insulin resistance

3.5.4.2.1 Beta cell function and mass

Scientific approach	Identify markers (in vitro, in silico), which detect early changes (preceding hyperglycemia) in beta cell mass in preclinical models and which predict diabetes progression and deterioration of metabolic control Use imaging technology with beta cell specific probed ligands
How it addresses the bottlenecks	Reduces the size and duration of in vivo and clinical studies.
Key players	UKPDS, Botnia, Euradia, Eurodia, Eugene2 network, JDRF, academic groups, industry, regulators
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre
Feasibility	Doable, extensive
Resource allocation	€ 33 million
Metrics of success	Validation in the in vivo models and in clinical studies
Generic issues	Biomarker centre, imaging centre
Interaction w/ SRA	Knowledge Management

3.5.4.2.2 Insulin resistance

Scientific approach	Identification of factors (in vitro, in silico) a) to correlate with insulin resistance in whole body or in specific tissues (muscle, fat, liver), or b) which can be used as prognostic tools for individuals (e.g. obese), who are at risk to progress from insulin resistance to type 2 diabetes, and c) which are reversible with therapy.
How it addresses the bottle-necks	Reduces the size and duration of in vivo and clinical studies
Key players	As in 2.1
Infrastructure needs	Patient databases, bioinformatics centre
Feasibility	Doable, extensive
Resource allocation	€ 27 million
Metrics of success	Validation in the in vivo models and clinical studies
Generic issue	Biomarker centre
Interaction w/ SRA	Knowledge Management

3.5.4.2.3 Validation of biomarkers for beta cell function, mass and insulin resistance in vivo and in humans

Scientific approach	1. **Beta cell**. Correlate the markers with beta cell function, mass and morphometry first in preclinical models. Thereafter validate the markers in humans with diabetes progression and with the efficacy of therapeutic approaches. 2. **Insulin resistance**. Demonstrate a correlation between the markers and insulin mediated glucose utilization in specific tissues (liver, muscle, adipose tissue), and in whole body in preclinical models and in humans.
How it addresses the bottle-necks	Validated biomarkers allow reduction in the size and duration of in vivo and clinical studies
Key players	Industry > academy, regulators
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre
Feasibility	Doable
Resource allocation	€ 25 million
Metrics of success	Validation
Generic issues	
Interaction w/ SRA	Knowledge Management

3.5.4.3 Characterization of focused patient groups for clinical trials.

Scientific approach	Using genomics and biomarkers to characterize European subpopulations prone to diabetes, and in patient groups those prone for beta cell loss, insulin resistance and micro- or macrovascular complications
How it addresses the bottlenecks	Use of pharmacogenomic markers to predict/select responsive patients will help to reduce the size and duration of clinical trials. Allows also preventive trials. This would be a great competitive advantage compared to low cost countries.
Key players	Patient organizations, academy, industry, SMEs, regulators
Infrastructure needs	Patient databases, bioinformatics centre
Feasibility	Difficult, requires novel technologies and ethical and political agreements
Resource allocation	€ 32 million
Metrics of success	Tailored medicine
Generic issues	Gene banks, biomarker centre.
Interaction w/ SRA	Knowledge Management, Education and Training

3.5.4.4 Quality of life

Scientific approach	Develop quality of life measures that capture drug efficacy beyond primary efficacy endpoints and which could also predict overall health benefits of novel therapies. Develop patient reported outcome tools to quantify therapeutic measures (home blood glucose monitoring) and endpoints (hypos, HbA1c, impact of diabetic complications on daily living etc).
How it addresses the bottlenecks	Quality of life data will help the regulatory approval of novel drugs. Facilitates patient recruitment.
Key players	Industry, regulatory, patient groups
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre
Feasibility	Doable
Resource allocation	€ 12 million
Metrics of success	Reduced expenses and lost working days
Generic issues	
Interaction w/ SRA	Knowledge Management

3.5.5 Resources

The total costs of the recommendations (€ 264 million) are estimates for a period of 7 years and will be subjects to further analysis as appropriate.

1. Develop more predictable preclinical models (in vitro, in vivo, in silico) for diabetes and its complications. € 44 million
2. Identify and validate novel targets in diabetes by discovery research in the pathophysiology of the disease and its complications. € 91 million

3. Identify and validate biomarkers for beta cell function and loss, for insulin resistance and for diabetic complications. € 85 million
4. Characterize subpopulations and patient groups using genomics and biomarkers for focused therapeutic and preventive studies. € 32 million
5. Develop Quality of live and Health Economic metrics to measure impact of novel treatments on daily activities and the economic benefits of novel therapy € 12 million

3.5.6 List of contributors

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4 Knowledge Management

4.1 Summary

A detailed analysis of the scientific and functional requirements of the Innovative Medicines Initiative was performed, together with an analysis of current state-of-the art in terms of technological infrastructure, data resources, data representation and exchange standards, and ontologies[22]. From the technical point of view, the requirements can be met using a distributed/federated, multi-layer, service oriented, and ontology driven architecture. However, severe gaps were identified, notably in the area of data representation and exchange standards, ontology development, data protection, and text mining. A set of generic research and development projects is proposed, in order to bridge these gaps and meet the requirements.

The main recommendations concerning Knowledge Management (KM) are:

- Set up one or more task forces to look at cross-disciplinary aspects (e.g., modelling of physiological processes), validate specifications, and align priorities,
- Set up a KM overview team to coordinate the support of individual projects, define standards of compatibility across projects, promote sharing of suitable KM technology, and provide context for generic technology development,
- Set up a Specific Support Action to evaluate the investment required to build the core of a back-bone ontology. This core could serve as an initiator for the definition of services, logical layers and abstraction layers,
- Develop enhanced standards for data protection in a web services environment,
- Develop standards and models for exposing web services (semantics), scientific services, and the properties of data sources, data sets, scientific objects, and data elements,
- Develop enhanced knowledge representation models and data exchange standards for complex systems, presently largely lacking, inconsistent, or incomplete, looking for synergies with current initiatives,
- Develop new, domain-specific ontologies, built on established theoretical foundations and taking into account current initiatives, existing standard data representation models, and reference ontologies,
- Develop advanced text mining tools for capturing implicit information about complex processes, as described in patents and literature, beyond and above simple pair-wise relationships between entities,
- Build a core reference database of validated experimental data extracted from the literature,
- Design standards for and build an expert tool (ontology/schema/rules negotiator) for exposing the properties of local sources in a federated environment,
- Design standards for and expert tool (services/data negotiator) to guide users through the complexities of the data, data models, simulation and modelling tools, etc.

4.2 Introduction

The goal of this chapter is to provide input on the technology required to establish a Knowledge Management (KM) environment capable of supporting the scientific objectives of the Strategic Research Agenda, to identify gaps in current technologies and to offer recommendations on how to bridge those gaps.

Throughout this chapter, we address a somewhat restricted aspect of Knowledge Management, which is the set of technologies and processes required to process data and information, thus allowing knowledge

[22] An ontology is defined as “an explicit formal specification of how to represent the objects, concepts, and other entities that are assumed to exist in some area of interest and the relationships that hold among them” (dli.grainger.uiuc.edu/glossary.htm). Ontologies are used for a variety of purposes, including inductive reasoning, classification, and problem solving, as well as to allow semantic interoperability of applications.

creation, sharing, and reuse. The focus is thus on enabling technologies, independent of any specific scientific requirements, and excluding both the organizational and cultural aspects of Knowledge Management and the purely scientific issues raised by the Strategic Research Agenda.

A multidisciplinary group with broad collective expertise in all areas of Knowledge Management was set up to review the scientific / business objectives of the Innovative Medicines Initiative, translate them into technical requirements, analyse the current state of the art, identify gaps and define strategies to meet the objectives. This group met in a series of workshops held in Brussels and Oxford. It became immediately clear that the required flexibility could only be met by a federated, multilayer architecture in which independent components, data sources, scientific services, *etc.*, could be configured dynamically and articulated by rules and ontologies. In such a configuration, three areas were identified as critical, namely:

- Technical infrastructure and services,
- Knowledge representations and models,
- Data sources and properties.

A detailed analysis of potential roadblocks associated with these three areas was carried out by break-out groups between formal workshops.

4.3 Summary of scientific objectives

Advanced technologies (*e.g.*, high-throughput screening, genomics, proteomics, metabonomics) have resulted in data generation on a previously unknown scale. Information derived from this data is extensively used in research and development, for example for target identification and validation, formulation of hypothesis, identification of specific pathways associated with disease states, diagnosis, monitoring, *etc.*

Also, there is a huge reservoir of proprietary data, both in companies and regulatory bodies, on active and discontinued products as well as on marketed products, covering the full scope of R&D. This includes any data from chemical structures to toxicity studies and clinical trial data. These data sets provide invaluable research tools. They could be pooled, possibly supplemented by data extracted from patents and literature, to increase the predictive power of current models, to revisit and to improve current models, and to populate newly developed models.

The emerging systems biology approach, aimed at understanding complex physiological and pathophysiological processes, requires both data integration at the molecular level (*e.g.*, “omics”) and the availability of sophisticated mathematical or computational models at the pathway, cellular, organ or disease physiology levels (so-called multiscale models). Although such modelling efforts are still in their infancy, they are rapidly maturing and some integrated computational models are already in use[23].

These new approaches will support specific needs from the safety and efficacy workpackages, as described in other sections of this document. For the safety workpackage, this includes the use of modelling approaches to support the prediction of a safe starting dose for the Entry into Human (EIH) study and the estimation of an acceptable therapeutic window, as well as development of predictive safety models, combining, for example, in silico data, ‘omics data, in vitro and in vivo toxicity. Similar approaches are also proposed in support of the efficacy work package, for example to reconstruct the behaviour of a system by integrating a given set of experimental data with prior knowledge of a disease’s physiology.

Within the scientific scope of the Innovative Medicines Initiative, areas of common interest should be identified, and all relevant information captured and shared. These areas could involve diseases such as diabetes, cancer or inflammatory diseases, toxicological targets such as the liver, bone marrow or the heart but also pharmacokinetics / metabolism and drug-drug interactions. Relevant models should be identified and, when necessary, new ad-hoc models developed. However, the development of such models is a complex task, limited by lack of integrated scientific knowledge. As a result, developing these models can only be undertaken in a goal-oriented, focused manner, by collaboration of scientists from different disciplines.

[23] See, for example, http://www.nature.com/nbt/journal/v22/n10/full/nbt1017.html for an excellent review of systems biology and drug discovery, the site of CellML http://www.cellml.org/, and the site of Entelos http://www.entelos.com.

From the Knowledge Management point of view, the requirements can be translated as follows:

- Capacity to search, query, extract, integrate and share data in a scientifically and semantically consistent manner across heterogeneous sources (public and proprietary) ranging from chemical structures and "omics" to clinical trial data,
- Capacity to integrate and share scientific tools (*e.g.*, modelling, simulation) as modules in a generic framework and apply them to relevant dynamic data sets,
- Expressive data representation and exchange standards,
- Dynamic and customizable configuration of applications,
- Encapsulation of validated physiological models, when applicable,
- Flexible, secure (covering all aspects of data protection encountered in a biomedical context), and scalable IT infrastructure.

A close integration with the scientific projects is a prerequisite for successful knowledge management. We therefore propose that KM staff be assigned to every project, providing close scientific support, and at the same time belong to the KM overview team, thus insuring consistency across projects.

4.4 Technical objectives

As summarized above (and described in details in other sections of this document), the scientific and functional requirements are extremely broad and diverse, in terms of specific goals, users, data sources, simulation and modelling tools, *etc.* The data resources to be federated by the platform are also characterized by a deep heterogeneity in term of source, ownership, availability, scientific content, quality, level of curation, database design, data organization, semantics, *etc.* They will expand over the lifetime of the project and will be used for simulation, modelling, navigation using a variety of methods, some of them likely to emerge as new science is developed. This diversity and the complexity of underlying science, as well as the complexity of applicable knowledge representation schemas and applicable scientific algorithms are also likely to increase with time.

From the users' point of view, the knowledge management platform must provide relevant, simple and intuitive access to information (search and navigation) and to services, provide precise organization of the content independently of sources, allow scientifically relevant data integration (data pooling) and data exchange, provide mechanisms for data capture and annotation, and provide knowledge sharing and collaborative tools. In addition, it must provide a dynamically evolving set of validated data exploration, analysis, simulation, and modelling services. Finally, it must be consistent with the way community participants work and integrate smoothly in their day-to-day environment.

In addition to sharing data, application, and services, the platform must enable community collaboration: collective working, virtual meetings, knowledge sharing, forums, discussions, *etc.*, open to whole community, as well as within context-defined sub-communities. It can take a simple form, such as finding relevant information in global resources or locating an expert, to complex interactions in a long running collaboration between a set of actors in a secure sub-section of the platform.

From the technical point of view, the platform must insure seamless data integration across a broad range of heterogeneous resources; interoperability of computing services and applications (semantic, scientific, and technical) across organizations and networks; secure and robust mechanisms for data and services management; and a flexible, intuitive, collaborative environment.

Further, the technical architecture must be generic enough to fit with almost all the existing technical solutions (both in term of hardware and software) and data sources, accommodate existing and emerging data representation standards, and be scalable and flexible enough to satisfy unpredictable requirements as they emerge. The architecture must be modular in order to support integration of new resources in a standardised way (*e.g.*, new data sources, new models, new ontologies, new scientific algorithms, new visualisation tools).

Finally, it needs to take into accounts some essential constraints, notably:

- It has to be technically feasible over a 5-year horizon,
- It has to be both open to multiple actors/organisations and highly secure.

In principle, the required flexibility of the future platform can be met by designing a federated environment articulating independent tools, components, and resources, based on open architectural standards, customizable, and capable of dynamic reconfiguration.

4.5 State of the art and gaps analysis

This section analyses the current technologies, best practices, and gaps in terms of:

- Technical infrastructure and services,
- Data resources and properties,
- Knowledge representations.

4.5.1 Technical infrastructure and services

Based on the analysis of requirements and constraints and on the analysis of current state of the art, it is likely that the platform will be designed around a distributed/federated, service oriented, and ontology driven architecture. To provide high flexibility, a multi-tiers services approach is preferred, with implementation of the following independent layers:

- Infrastructure: defines the whole of hardware and software components that support basic operations and provide such functionality as availability (Quality of Service), data integrity, *etc.* (*i.e.*, firewalls, redundant systems, backup infrastructure, computer clusters, etc.),
- The backbone: comprising a set of services providing basic functionality and interoperability (*e.g.*, messaging, brokering). The backbone is also in charge of managing services and data access (security),
- Data access to heterogeneous resources could be provided through two sub-layers:
- Data virtualization layer: to decouple data from their local schema and make data access platform- and schema-independent,
- Data abstraction layer, to provide a common view of all accessible data via a set of ontology / rule-mapping mechanisms,
- Services layer, making services (core, administrative or scientific services) accessible over the backbone and connecting to data resources,
- Connections layer, providing a secure access point to all authorized users and processes,
- Organizations, describing users and allowing them to share data, share services, and collect information.

Application Management

The most appropriate current technology providing the required flexibility is web services. However, it should be noted that current technical web services description standards are inappropriate for selection based on the scientific tasks they are supposed to be used in. Therefore, we suggest that emphasis should be placed on necessary improvement of web service descriptions and annotations (see below). For practical reasons, common services may have to be hosted centrally. However, applications may not always be readily accessible as web services and, in some cases, instead of developing complex interfaces, it will be more efficient to use a message broker system (one connector per application: requester and provider associated to a message hub system managing the exchange). Also, some partners may want to share specific services and algorithms with the rest of the community and a specific area where services can be published and managed will required. This service could be delivered, for example, by using a “business to business” (B2B) platform, a mechanism that could also be used for data exchange.

Data Management

The data management layer has to provide a single access point to heterogeneous data resources in different data formats. This can be implemented via a data virtualization layer, insuring data format independence and data presentation layer, insuring customizable, scientifically consistent representation.

Security Management

Security will have to be addressed at the levels of:

- Infrastructure security,
- Application access,
- Data Protection,
- Access Control (policy-governed),
- Privacy Enhancing Technology (e.g., de-identification).

Security and privacy are active areas of research and technologies are emerging that could be used to insure the security of the platform. Data de-identification, required in some cases for privacy or Intellectual Property reasons, could take place at the partner site rather than at the central gateway to avoid the transit of identified data on the network and potential security failures. An alternative, although legally challenging, would be an off-site Trust Service offering de-identification services.

The functional architecture discussed above is summarized in the following graph:

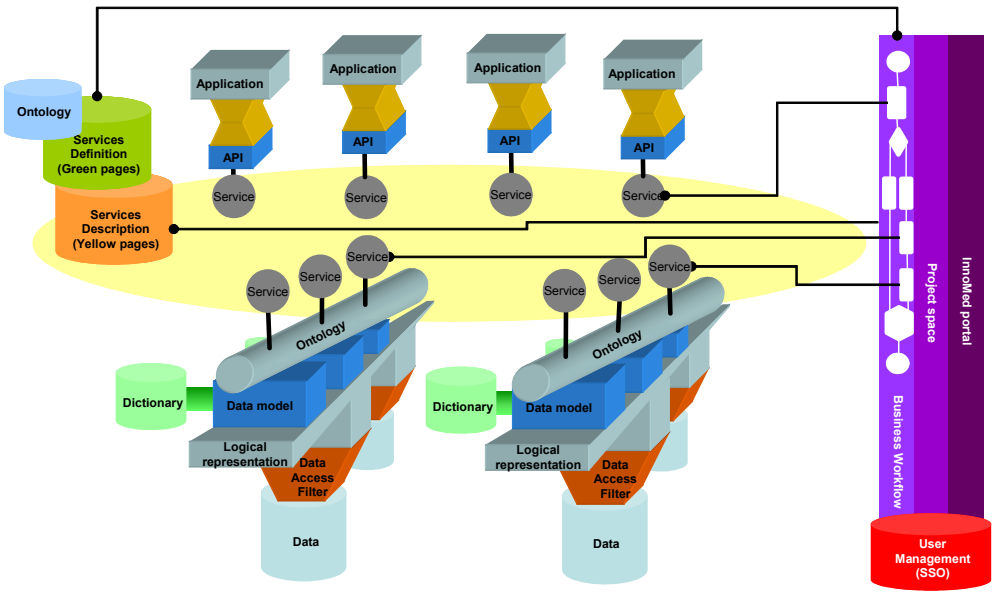

Figure 16: Functional architecture

4.5.2 Data resources

Data integration

The data described by the scientific requirements is extremely heterogeneous. It can be broadly classified into three categories:

1. Experimental proprietary data owned by companies, universities, hospitals, *etc.*
2. Highly curated, experimental-quality public domain data which can be extracted, for example, from publications and patents, or resides in reference databases (*e.g.*, SwissProt, PubChem)
3. Publicly available, qualitative, documentary data such as literature and patent databases (Medline, WDI, CAS), sequence databases (), chemical structures databases (CAS, Beilstein), or full text documents.

Data belonging to category 1 and 2 can be pooled for data analysis, data mining, simulation, modelling, *etc.*, under the assumption that it would be possible to apply relevant transformations to build composite data sets that are consistent in terms of data content, data quality, data descriptions, and mathematical properties with the scientific objectives and algorithms to be used.

Data belonging to category 3 can be used for qualitative data analysis and exploration, etc. but not for scientific computations.

The aggregation of composite 'experimental' data set from heterogeneous sources requires that strict rules be applied (a) to validate data, (b) to evaluate the alignment of the data with the scientific objectives and (c) to apply relevant transformations. Critical to these rules is a detailed description of the underlying data sources: how were the data obtained, for what purpose, what is its quality/validation level, how complete is the data set, what is the bias of the data set, what are the standard errors of the measurements, what protocols were used, *etc.* In the data exchange formats that are currently under development, these aspects are poorly developed. That is, we do not have a standard specification sufficiently expressive for exposing properties in a generic manner to drive inference, data aggregation, computation of data set properties and data transformations. In other words, there is no mechanism for creating a virtual experimental data warehouse on-the-fly. This is particularly critical when attempting to build data sets bridging disciplines and linking, for example, pre-clinical and clinical data.

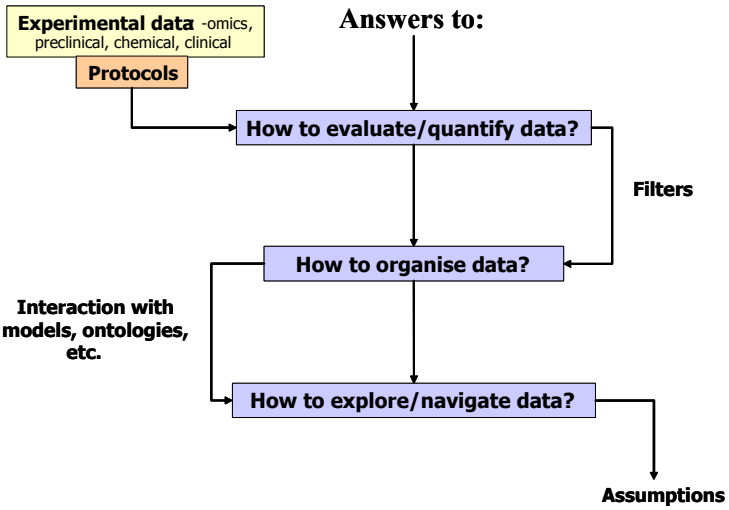

Figure 17: Data evaluation and transformation

Standard specifications should be developed, after an in-depth analysis of required properties (depending on data type, protocols, the real-world entities described by the data, *etc.*), aligning with current initiatives, *e.g.*, in the area of 'omics and clinical trials. Similar specifications are required to describe the "properties" of scientific services, in terms of data requirements, caveats, *etc.*

Data availability versus data quality

As mentioned above, the potential data coverage is extremely broad, and likely to expand over the lifetime of the project. It includes preclinical experimental data (in-vitro and in-vivo), data about chemical structures, genomics, proteomics, metabonomics, pathways, *etc.*, up to clinical trials data and data residing in patient records. At the same time, we are experiencing an explosion in the quantity of available data. In many cases, however, this data cannot be optimally used in a research environment. This is caused by the lack of interoperability standards, as mentioned elsewhere, but also because of widely varying level of (or lack of) data curation, quality control and normalization methods. This is also true, in many cases, for preclinical experimental data repositories. Data quality is critical and substandard data must be eliminated. This requires, at the very least, that recommendations be developed (with the various partners) and an index of quality (confidence) be assigned to each data element.

Interactive data aggregation

To insure flexibility and scientific relevance, a black box approach to data searching, data aggregation and analysis should be avoided. The whole process of data aggregation should be transparent and remain under the control of the scientist. The simple "wizard" approach to guide the user through the possible processes and workflow will probably fail: too many sources, scientific models and algorithms will have to be integrated are integrated into the platform. A new type of "Intelligent Wizard", possibly using inference engines and standard descriptions, will probably have to be designed.

4.5.3 Logical data layer – Knowledge Representations

The goal is to provide a simple, robust, yet flexible set of standards for consistent description and organisation of business entities across data sources and services. With a "business entity" (BE) we mean: an aggregate of data (or a representation) that describes some entity existing in reality that is relevant to the Innovative Medicines Initiative scope, examples being a protein, a tissue sample, an assay, a protocol, or some domain actor such as a research unit, a person, or even some information resource such as a document, a technical schema *etc.* We will refer to these entities in reality as "science objects" (SO). The set of standards to be provided must be articulated by ontologies describing the SO and their properties, and the relationships that obtain between Sos. Also the rules to be adhered to for ensuring quality data collections should be crafted by resorting to these ontologies. This is required for:

- Reliable and consistent information integration / consolidation across heterogeneous data resources,
- Consistent interaction with the data,
- Interoperability of services, at the semantic and technical level,
- Relevant configuration of the services.

From the system viewpoint, a BE is defined as an identified and reusable set of data, bearing consistent scientific meaning and to which specific properties and methods can be attached. Complex business entities can be assembled from a well defined set of complex or "elementary" business entities. For example, a (tentative) business entity describing an "assay result" will probably be composed of a compulsory set of elementary business entities describing science objects such as chemical entity, buffer, dilution, molecular target, protocol, species, strain, unit, *etc.*, each with specific types and properties

Each business entity is assigned:

- A set of attributes describing its *logical* properties, which globally define how a BE can be transformed, queried, navigated or otherwise processed,
- A set relevant *descriptive* attributes (*e.g.*, assay name, assay number, disease, chemical entity, *etc.*), which define what the business entity is about. From these examples, it is clear that the ontologies that support this, must take care of universals (types, classes, … examples being disease, chemical entity, …) and particulars (individuals, tokens, …, an examples being an assay number, the patient from whom data are obtained, …).

Together, these logical and descriptive attributes must be sufficient to describe the data element properties fully and unambiguously, to drive methods (calculations, translations, transcoding, transformations, *etc.*) applied to the data elements, and to search, navigate, explore, filter, aggregate data, *etc.*

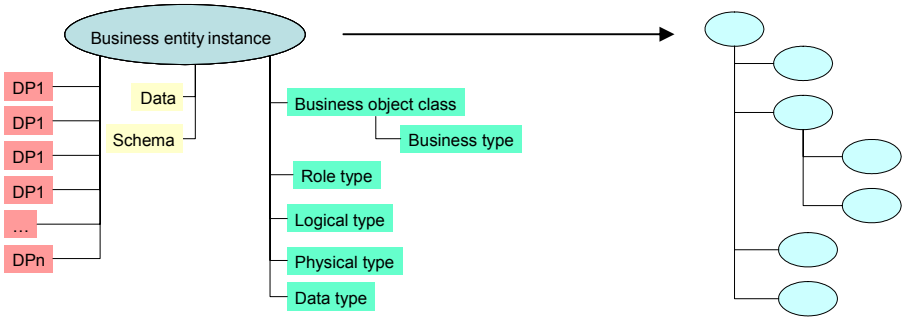

Figure 18: Business entities

*Green: logical properties; salmon: descriptive properties; yellow: data and associated schema

Independently of their logical and descriptive properties, business entities have to be uniquely identified in their original definition scope and across the whole system, and appropriate mechanisms have to be foreseen to keep track of the interrelationships between different business entities that describe the same science object. As an example, if the same test is applied twice to the same individual sample, it will lead to two numerically different business entities. The data that these BE contain will be very similar, but not nec-

essarily identical. Even so, the system should be able to be deal with BE that contain identical data, but are derived from different samples.

Four major classes of representations will be needed to support the platform functionality:

- two logical data representations:
    1. Business entities descriptions,
    2. Business types <----> logical types<----> rules (methods).
- and two science object ontologies:
    1. Facts (precise relationships between particular entities as described in experimental data),
    2. Descriptions of the universals that are instantiated by the particulars (semantic organization), business entities descriptions,

These representations and ontologies will be used for a variety of purposes, such as searching and mapping data from heterogeneous sources, data set navigation and exploration, data aggregation, and data visualisation. They will describe generic relationships, properties, restrictions and constraints, independently of any local context. Together, they will form the upper level "backbone business entity ontology" (BBEO).

For the most part, they will have to be developed, taking into account current initiatives, existing standard data representation models, and reference "ontologies" currently used in Life Sciences. Because of the broad coverage and complexity of the project and because of the critical issues of scalability, extensibility and integrity, it is of particular importance that applicable ontologies be built on sound theoretical foundations that take the differences between particulars and universals properly into account. Moreover, since the scope of the project encompasses an open list of various scientific domains not necessarily sharing common terminology, the BBEO will have to harmonise the descriptions of science objects on the basis of generic, broad, and cross-domain scientific concepts.

Local ontologies used to describe local properties, restrictions and constraints will have to be mapped to the BBEO. This will require each local source to expose its local ontologies (and logical schema, rules *etc.*) to the central repository via a mapping negotiator, to align and validate the different sources to a consistent composite view of the data (semantically, mathematically, and scientifically), and to configure the connector. The result will be a semantic hub mapping local attributes (plus associated definitions and rules) to the core ontology. Similar tools will be required to map the schema of the source database to the data federation tool.

Both "core" and "scientific" services can be driven by data source properties, BE properties (logical and descriptive) and by data sets properties (computed). Additionally, they can be dependent on:

- Semantic rules (relevance),
- Scientific rules (semantic properties of the data *vs.* requirements of the method),
- Mathematical rules associated with the method to be used (mathematical properties of the data set *vs.* requirements of the method).

These rules and dependencies should be implemented in an ontology driving an interactive "data negotiator" articulating data and services. Standards and specifications for exposing these rules are needed, building on current mediator technology.

Both the BBEO and local ontologies can be used to extract typed concepts and relationship between concepts in structured and unstructured external resources. The process involves zoning, parsing, normalization, lexical extraction, information extraction, *etc.*, and can be customized to provide a specific view of the domain.

4.6 Research and development areas

4.6.1 Comments on research projects and project management

Several of the issues addressed above, notably in the area of data integration and semantic interoperability, are the focus of several European Communities-founded, large-scale initiatives. These include notably:

- The INFOBIOMED Network of Excellence (NoE), focusing on biomedical Informatics, in particular on the development of methods for clinical and genetic data interoperability and integration and on interfacing tools and technologies used in both medical informatics and bioinformatics,
- Semantic Interoperability and Data Mining in Biomedicine NoE, also focusing on methods for bridging medical informatics and bioinformatics, data interoperability and data mining,
- More generic projects aiming at wide-scale adoption of semantic technologies, such as the two Knowledge Web NoE and REWERSE,
- Institutions have been created to deal with ontology in general, both in Europe (Centre for Ontological Research) and the US (National Centre for Ontological Research), and biomedical informatics in particular (IFOMIS),
- Commercial or open-standards organisations active in this field.

Synergies should be identified between the Innovative Medicines Initiative and these organizations and research efforts should be aligned. Similarly, an inventory of current initiatives on biomedical datasets, representation models, specialized applications, grid computing, semantic grids, *etc.* should be carried out.

- From a technical point of view, cutting edge architecture and currently available or emerging technologies have been identified as capable of supporting the scientific and technical requirements of the Innovative Medicines Initiative. Minor issues have been raised, included in the projects below,
- The technical platform must be properly dimensioned and its functionality closely aligned with the business needs, scientific requirements and priorities of the Innovative Medicines Initiative. We recommend that a task force be set up to look at cross-disciplinary aspects (*e.g.*, modelling of physiological processes), validate specifications, and align priorities.

It is equally important that specific projects (safety and efficacy), with their own KM support, be coordinated with the overall KM strategy. We therefore propose that KM teams supporting each safety or efficacy project also participate in a larger KM overview team, to insure coordination, help define standards of compatibility across projects, promote sharing of suitable KM technology, and provide the context for generic technology development work.

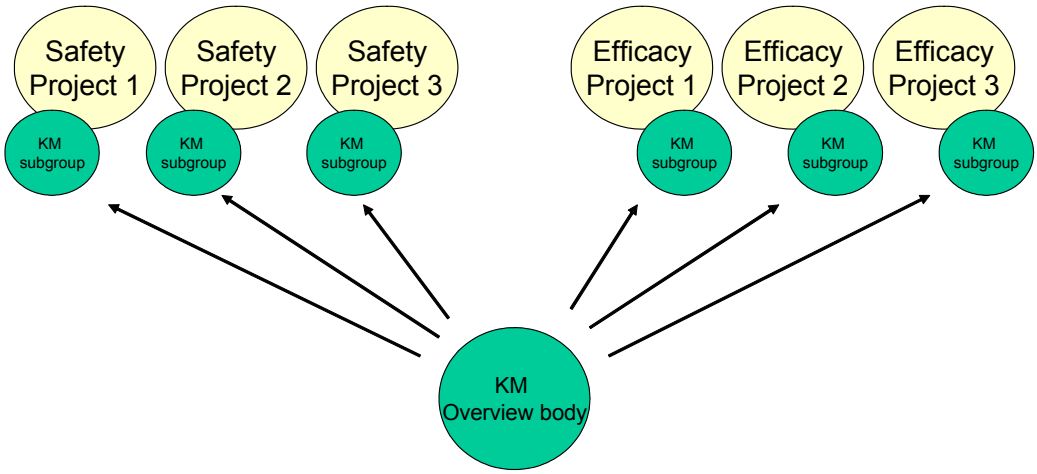

Figure 19: Knowledge Management projects coordination

4.6.2 Research projects

4.6.2.1 Core backbone ontology evaluation

The feasibility and quality of the project, and ultimately its scientific relevance, relies on high quality, robust, business-focused, scalable, state of the art ontologies. As mentioned above, these ontologies must be built on sound theoretical foundations for the solution to be viable and resilient. We therefore suggest that, as a preliminary to research projects, a Specific Support Action be set up to evaluate how much it would take to built the core of a backbone ontology. This core could serve as an initiator for the definition of services, logical layers and abstraction layers.

4.6.2.2 Security and privacy guidelines

Security and privacy issues are somewhat complex and largely outside the scope of KM per se. They could, however, have a significant impact on the KM platform (for example, when patient data are involved). Research in the area of electronic patient records has addressed a number of these issues in detail. We suggest that a project be launched to review these issues (legal, regulatory, ethical, intellectual property) and propose guidelines and specifications for implementation) in the context of KM.

4.6.2.3 Data protection standards in a web services environment

The technology for data protection (avoiding the strict separation between security and privacy issues as these are largely interwoven) in a Web Services context is not mature. Standards are still evolving, with implementations often falling behind (examples are SAML, XACML). We suggest a research project to evolve these standards to the required level.

4.6.2.4 Standards and models

Generic standards and models are lacking in the following areas (see discussion above):

- Web services definitions: semantic rich annotations of web services for service discovery,
- Rules and properties of core / scientific services,
- Data sources properties,
- Data set properties,
- Data element properties.

These standards and models (domain independent) are required for the articulation of data sources, core services (mapping, *etc.*) and scientific services. Developing all these standards, however, is a very large task and priorities will have to be set. In addition, generic standards need to be tested in reality. Therefore, integration of these activities (and testing of the proposed standards) with other research of the overall program is important.

4.6.2.5 Scientific knowledge representations

As mentioned above, the Innovative Medicines Initiative will rely in large parts on the availability of high-quality knowledge representation models and data exchange standards, presently largely lacking, inconsistent, or incomplete. We propose that a project be launched to design generic specifications and guidelines and to draw a road map, identifying synergies with current initiatives, and seeking harmonisation with other science areas currently addressing similar issues of semantic interoperability of scientific data. The focus should be on developing knowledge representations standards for complex systems, *e.g.*, systems biology, disease models, *etc.*, as well as research processes. Such research work will deliver templates for dictionaries and thesauri used in information extraction approaches.

4.6.2.6 Domain ontologies

The back-bone ontology as well as new domain-specific ontologies will have to be developed to describe the relationships between science objects both at the level of universals and particulars such that from these relationships that obtain in reality, adequate relationships at the level of the business entities can be derived. Because of the broad coverage and complexity of the project and because of the critical issues of scalability, extensibility and integrity, it is of particular importance that applicable ontologies are built on

sound theoretical foundations. However, this development must take into account current initiatives, existing standard data representation models, and reference "ontologies" currently used in Life Sciences, and the requirements for mediation between existing (and future) ontologies (see below)

4.6.2.7 Text and data mining

Current information extraction techniques are relatively successful at extracting entities and, to a lesser extent, simple pair-wise relationships between entities (e.g., protein-protein interactions). While this is extremely useful, more advanced tools are needed to extract implicit information about complex physiological processes described in patents and literature and required by computational models. Similarly, text mining techniques should be extended to information extraction approaches beyond the scope of current, biology-focused text mining (e.g., chemical entities), and enhanced to help in the extraction and validation experimental quality data from unstructured documents.

4.6.2.8 Data extraction and curation

Relevant experimental results published in the literature should be extracted, validated and made available to the community, thus greatly enhancing data pool. This process can be aided by automatic identification and extraction in full text documents. After identification of data elements to extract, a specific project should aim at building a core reference database of validated experimental-quality data extracted from the literature.

4.6.2.9 Ontology/schema negotiator

In a federated system, each data source is independent and connected to the system via wrappers, used for accessing and retrieving data. This requires a minimum set of information on the data sources, for instance the database logical schema, data elements, local ontologies, *etc.,* required for data integration. An expert tool for exposing the properties (including scientific properties) of local sources and mapping them to the core is required.

4.6.2.10 Data/services negotiator

As mentioned above, a black-box approach should be avoided and the scientist must remain at all time in full control of the process. At the same time, the interface to the system must be relevant, intuitive, and simple to use. This will require the design of a new family of "wizards", guiding the user into the complexities of the data, data models, simulation and modelling tools, *etc.*, in a goal-oriented, scientifically relevant and intuitive manner, possibly using inference engines and evolutionary algorithms. This includes the development or enhancement of semantic query languages.

4.7 Resources

The estimated costs of implementing the recommendations described in this chapter are: €13 million per year for a period of 5 years.

In addition, resources have been allocated for the IT infrastructure and support for safety applications (€15 million, page 29) and for efficacy applications (€21 million, page 101). It is anticipated that many individual research projects ultimately funded by this initiative will have unique IT/KM needs that will be funded as a part of these budgets.

In total, €49 million per year are therefore allocated for the development and implementation of the knowledge management part of this SRA.

4.7.1 Operations

Project support and management

- Five FTEs 750 k€
- General support 500 k€

Infrastructure (hardware and software)

- One-off cost - first year (central gateway) - 1 central site and 3 distant sites 5'100 k€
- Following years 2'550 k€
- Seats (1000 users) 2'000 k€
- Total per year 5'060 k€

Licences, applications & development

- Ten development/analytic platforms 4'000 k€

Total Operations (per year) **10'310 k€**

4.7.2 Research projects

These development projects need to be initiated as soon as possible and most of the costs will be incurred during the first two years of the initiative.

Research Project	Duration (months)	Total costs over 5 years (k€)	Per year cost (k€)
Core backbone ontology evaluation	6	540	108
Security and privacy	6	540	108
Data protection standards	6	540	108
Standards and models	12	1'080	216
Scientific knowledge repre-sentation	12	1'080	216
Domain ontologies	24	2'160	432
Text and data mining	24	2'160	432
Data extraction and curation	60	3'750	750
Ontology/schema negotiator	12	1'080	216
Data/services negotiator	12	1'080	216
Total Research Projects			**2'802**

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5 Education and Training

5.1 Summary

Based on consultation with stakeholders, the E&T work stream has identified a number of gaps within education & training in support of the medicines development process. A SWOT analysis has been made resulting in a number of recommendations.

The scope of the activities within E&T is to establish the European Medicines Research Academy (EMRA). EMRA is a pan-European platform for education and training covering the whole lifecycle of a medicine. EMRA supports current and future professionals involved in biomedical R&D including regulatory officers. Further, the platform should provide the basis for information on the medicines development process, including the rules governing the process, to stakeholders who are not directly involved in the process, e.g. journalists, venture capitalists and patients. To complete the loop, patients should be involved as these can make a contribution to the determination of what and how the professionals acquire skills and knowledge.

The EMRA should be based on existing centres of excellence within the relevant disciplines. It is not intended to build a parallel system for E&T to the existing universities and higher education institutions. The activities in the E&T work stream have close links to the activities in the “Bologna process” to establish the European Higher Education Area by 2010.

The activities suggested have been prioritised, the top priorities are:

1. Establish the EMRA including a central coordinating unit and an advisory E&T council.
2. Establish programmes for integrated medicines development and for ethics committees and patient organisations.
3. Establish programmes for safety sciences, scientists within pharmaceutical R&D and Pharmaceutical Medicine professionals
4. Establish regulatory affairs based programmes
5. Establish programmes for Bio-statisticians, Bioinformaticians and biomedical informaticians.

It is proposed to establish the programmes in 4 regions of Europe and courses are to be held twice a year. In parallel with these activities other activities are needed. These include establishment of criteria for centres of excellence and identification of these, options for closer collaboration between academia and industry in terms of E&T including an incentive system to facilitate mobility, re-evaluate the evaluation process for academicians, open dialogue with EU member states on curricula including establishment of European criteria for curricula, development of an accreditation system for E&T, mapping existing Public-Private-Partnership in E&T and identifying existing relevant European curricula.

It is important to realise that medicines research and development require a trans-disciplinary approach involving many of the traditional scientific areas within life sciences and in addition technological areas e.g. biotechnology, nanotechnology, medical technology and IT.

5.2 Introduction

The objective of this chapter is to describe identified gaps related to education and training in the medicines development process. Further to discuss how to bridge these gaps to align with the requirements of the process to provide new medicines for the benefit of patients, science and society.

The EU has a great potential for innovation because of its excellent science, education and training base. However, the EU is lagging behind because of lack of adequate funding, insufficient coordination of efforts and resources, weak strategic intent, as well as inability to react with sufficient speed and force on new challenges and opportunities.

The Strategic Research Agenda will propose changes to the way contemporary medicines R&D is performed. The identified gaps and bottlenecks will be addressed by new technologies and new paradigms for assessment of safety and efficacy as well as for medical practice. This also calls for identification and addressing gaps and bottlenecks that exist in the Education and Training (E&T) of scientists within life sciences who will be, or are, involved in the medicines development process. Further the consultation with stakeholders during the creation of this SRA has revealed a need for insight in the medicines development

process for people indirectly involved in the medicines R&D process, including patient organisations and the public.

Definition of E&T:

In the context of Innovative Medicines for Europe, Education & Training is defined in the following way[24]:

- Education encompasses teaching and learning specific skills, and also something less tangible but more profound: the imparting of knowledge, good judgement and wisdom,
- Training is the teaching of vocational or practical proficiency and relates to specific useful skills.

5.3 Gap analysis

5.3.1 General gaps

Following consultation with stakeholders in workshops in February, April and May 2005[25] an analysis of the gaps within education & training in support of the medicines development process has been carried out. The gaps are covering three groups of knowledge; *overview, specialist and bridging* and a number of *specific gaps*.

Many of the players involved in the medicines R&D process need a *integrated overview* of the entire process, however at a variety of levels. For specialised professionals, e.g. managers, project managers and project team members, it is important that these have an understanding of the interdisciplinary aspects of Pharmaceutical R&D and the requirements for the down-stream process towards availability of the medicine to the patients within all three main topics of the regulatory dossier, non-clinical, clinical and quality (CMC[26]). A high level, "helicopter view" is essential for many stakeholders in the process, e.g. regulatory authority personnel, clinical investigators, university teachers, ethics committee members, journalists.

For *specialists* there is a profound need for qualified personnel within the natural, technical, pharmaceutical and medical sciences. Further there is a need for ongoing training to keep updated with scientific and technology developments.

With respect to *bridging* there is a need for training of specialists who require knowledge from another scientific area than the one they graduated from.

5.3.2 Specific gaps

The specific gaps identified include:

- The current organisation of universities facilitates building of "silos" where each scientific area lives its own life without much interaction with other areas. This is contributing to the fragmentation of European research[27,28],
- In most European countries the scientific interaction between scientists in academia, industry and regulatory authorities are minimal and often the movement of intellect is uni-directional towards the industry. A situation where there is a flow of expertise between the 3 parties will facilitate share and exchange of knowledge,
- Translational science from basic and non-clinical research to the clinical sciences. Often there is little or no interaction between clinical scientists and e.g. human biologists even they may work on the same scientific topics. This gap is critical and is yet not bridged. Translational medicine is

[24] Source Wikipedia, The Free Encyclopedia, http://www.wikipedia.org

[25] Reports from workshops, E&T1, E&T2, E&T3 are available on the Innovative Medicines website: http://europa.eu.int/comm/research/fp6/p1/innovative-medicines/index_en.html

[26] CMC: Chemistry, Manufacturing and Control

[27] Wilson EO, Consilience: The Unity of Knowledge. ISBN: 0679450777

[28] Busquin P, At the 'Communicating European Research' conference on 11 May 2004 http://ica.cordis.lu/search/index.cfm?fuseaction=news.simpledocument&N_RCN=22027&CFID=994044&CFTOKEN=61399528

emerging as an attempt to bridge this gap from "bench to bedside" – and back again by combining a thorough understanding of the biology of a disease with the clinical picture[29].

- Scientists are urgently needed within these specific areas:
  - There is a need for safety scientists with a much broader spectrum of knowledge than the traditional toxicologist. The future safety scientist will have to integrate knowledge accumulated from many safety-relevant disciplines (e.g. primary and secondary pharmacology, functional genomics, safety pharmacology, physiology, pathophysiology, physical chemistry, animal and clinical toxicology, cellular biology, biochemistry and animal physiology with all their special branches) to excel in modern risk assessment and risk management[30],
  - Pharmacology, non-clinical and clinical,
  - Physicians specialised in pharmaceutical medicine,
  - Bioinformatics, biosimulation, Knowledge Management, Systems Biology, Systems toxicology and Systems Pharmacology and physiology (in vivo whole organism) and in-silico modelling,
  - Medical statistics/Biostatisticians,
  - Medical imaging is being used more and more both in basic research and in clinical research. A need is identified both in terms of trained scientists and technicians and in access to the technology, which is expensive to establish. This issue is dealt with in the efficacy part of the SRA.
- Establishment of a curriculum for medicines development for professionals needing profound insight in the process,
- Continuous professional development including update on new scientific developments and technologies for scientists, physicians, patients and carers,
- Faculties and undergraduate students are not realising the career opportunities within biomedical R&D. Especially within e.g. Vet Medicine, Pharmacy, Biology, Medicine the focus is on the traditional career paths,
- Implementation of the Clinical trial (GCP) directive[31] causes a need for training of regulatory personnel for GCP inspections, clinical investigators, monitors, clinical research associates, patients and people working for patient organisations and ethics committee members. A thorough understanding of the rules governing clinical research is a prerequisite for Europe to keep, and possibly strengthen, its position within clinical research,
- People working in Small and Medium Enterprises (SME), especially in the early phases of medicines R&D, need business skills and understanding of the business environment,
- Journalists, venture capitalists and the public lack understanding of the conditions for and the process of medicines development,
- Patient organisations have substantial knowledge of specific diseases and patient needs. This knowledge should be utilised in the medicines R&D process,
- European education needs to strive for excellence and competitive systems have to be put in place for a continuous improvement of the scientific level in Europe.

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[29] Mankoff SP & al, Lost in Translation: Obstacles to Translational Medicine, Journal of Translational Medicine 2004, 2:14

[30] EUFEPS 2004, Report from EUFEPS Brainstorm Workshop on Safety Sciences, Brussels, April 2-3 • 2004

[31] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=32001L0020&model=guichett

5.4 Recommendations

In the process of stakeholder consultation in the development of this SRA it became clear that the diversity, cultural and language differences within Europe represent both strength and a weakness. The strength represents an opportunity for viewing a challenge from a multitude of angles. The weakness is caused by the same diverse scientific, cultural and linguistic backgrounds resulting in conflicts based on misinterpretation and misunderstandings.

European strengths:

- Strong biomedical-relevant research, which is the basis for education and training,
- A strong presence of academic research in the field of pharmaceutical sciences,
- European research groups develop new concepts and can successfully compete with leading groups in the USA/Canada and Japan/Korea/Taiwan,
- Existing high quality postgraduate courses in pharmaceutical medicine in UK, Spain, Belgium, Sweden, Germany and France that are sought by professionals from outside Europe,
- Pharmaceutical and clinical sciences has a number of internationally highly visible scientists, who act globally as leaders in the field,
- Europe has a good infrastructure to facilitate research e.g. clinical trials,
- Cultural diversity provides an opportunity for viewing a challenge from a multitude of angles,
- Europe still has a strong presence of biomedical industry.

European weaknesses:

- Lack of funding for research,
- Lack of coordination of funding programmes for life science research,
- Europe is “separated by multiple languages” and the cultural diversity mentioned above. Few European scientists for whom English is not their native tongue master English to the same level as their mother tongue,
- Mobility: Despite mobility programs offered by the EC, exchange of students and researchers within Europe is bureaucratic and not optimal,
- Mobility: Attracting gifted young scientists from countries outside the EU is even more difficult,
- The public perception of the players, industry, regulators and scientists has deteriorated over the years resulting in increasingly strict regulations and resistance in the public towards introduction of new molecular biological findings (fear of the unknown),
- Critical mass: Europe has many high quality universities and higher education institutions but individually they are too small and in many cases locally, -not European focused. Only few examples of transnational collaboration within E&T exists[32],
- Introduction of new technologies is slow,
- Recognition of the importance of transdisciplinary research is limited,
- Intellectual property: To obtain a European patent is much more difficult than e.g. a US patent, especially for SMEs.

Opportunities:

- Many European organisations including the European Commission, national states, industry organisations, patient organisations and learned societies have realised the weaknesses as illustrated by this SRA,

[32] ULLA: European University Consortium for Pharmaceutical Research, http://www.u-l-l-a.org

- Political focus: With political will and adequate financing, Public-Private-Partnerships could overcome some of the weaknesses,
- Europe has the expertise to re-engineer the medicines R&D process to the benefit of science and society.

Threats:

- The emerging economies in China and India could move high level research and thereby education and training to their areas,
- Loosing even more biomedical industry in Europe,
- "Silo" thinking within all groups of stakeholders,
- Lack of political will to do what needs to be done.

To ensure a common understanding of the scope of the E&T activities the following vision and mission for the endeavour have been worked out.

Vision

This vision provides a view of the European future for Education and Training related to the medicines R&D process.

By 2013 the European Technology Platform for Innovative Medicines will have established the European Medicines Research Academy (EMRA), a virtual pan-European platform for education and training for professionals involved in biomedical R&D including regulatory officers over the whole lifecycle of a medicine. The platform will include programmes for E&T covering the horizontal layer of integrated thinking over the entire medicines R&D process combined with specialised courses linked to the format for a registration dossier: non-clinical, quality and clinical as illustrated in figure 20. Further, the platform will provide the basis for information on the medicines development process, including the rules governing the process, to stakeholders who are not directly involved in the process, e.g. journalists, venture capitalists and patients. By 2013 the activities suggested have been implemented and results of this are emerging. The ovals will be populated with existing and new courses where some may be used both at a general level and at a specialised level.

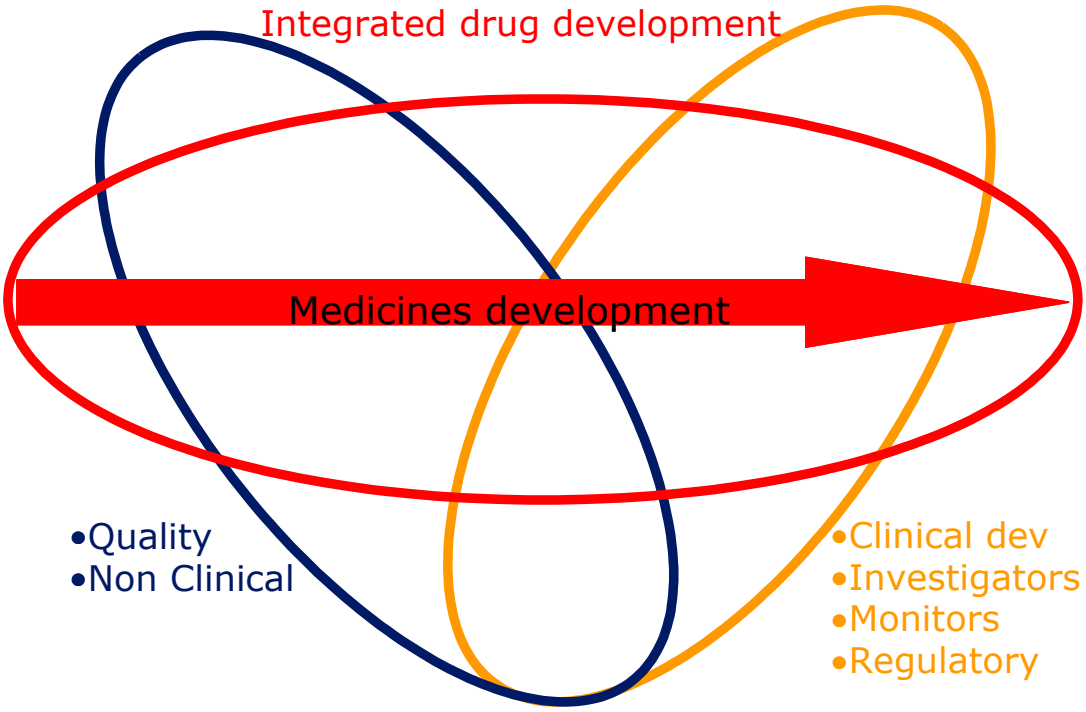

Figure 20: Organisation of the E&T platform.

Organisation of the E&T platform in streams, integrated overview (red) and specialist within clinical non-clinical and quality/CMC (blue and yellow)

The development of the E&T platform is in parallel with and supported by the Bologna process by which the European Higher Education Area[33] is established in 2010 as a result of the 10 action lines from the Bologna process[34]:

- Pan-European comparable degrees based on a 2-cycle system,
- An established ECTS[35] system of credits,
- Increased mobility of students and university staff,
- Established quality assurance standards for education,
- Implemented lifelong learning strategies,
- Active involvement of stakeholders of higher education,
- Attractiveness of European higher education to students from Europe and other parts of the world,
- A clear link between the European Higher Education Area and the European Research Area linking undergraduate, graduate, doctoral and postdoctoral[36] education and training.

[33] http://www.eua.be/eua/en/Research_linking.jspx

[34] http://www.bologna-bergen2005.no/EN/BASIC/Pros-descr.HTM and http://www.bologna-bergen2005.no/Docs/Norway/041014Fact_Sheet_Bologna-Process.pdf

[35] ECTS: European Credit Transfer System. http://europa.eu.int/comm/education/programmes/socrates/ects_en.html

[36] Postdoctoral in this context means after obtaining a PhD

Mission

The mission defines what the E&T platform will be doing in the future described in the vision. The E&T platform will:

- Build upon existing universities and higher education institutions in Europe by identifying centres of excellence within the various disciplines of medicines R&D and stimulate collaboration between these centres,
- Provide E&T support to remove bottlenecks in the medicines R&D process,
- Establish multiple public-private partnerships within E&T within graduate, doctoral and postdoctoral education and training,
- Facilitate mobility between academia, industry and regulators,
- Help to create biomedical R&D leadership for Europe to benefit patients and society.

Key objectives

The key objectives define what to be achieved going forward:

- Establish a co-ordinating council with representation of the relevant stakeholders[37] and with expert sub-groups to assess the availability and quality of training in non-clinical, clinical, quality (CMC) and integrated drug development. This activity includes mapping of availability and contents of existing courses,
- Assessment of institutions already involved in E&T and audit of E&T activities within disciplines,
- Identification of centres and institutions with appropriate expertise to deliver courses and training,

Overcome “silo” thinking. Pharmaceutical research is best done in a transdisciplinary approach.

  - However, many researchers are still thinking in disciplines in order to “protect” their fields,
  - Activities to make researchers realise that a combination of expertise improves research and innovation,
  - Stimulation of trans-disciplinary E&T, e.g. combination of pharmacist/chemical engineer, medicine and technology.

- Overcome the language barrier, English is used for textbooks and courses in all participating universities and higher education institutions[38],
- Harmonisation of E&T on a European level to create a European Community of Pharmaceutical and Medicines Researchers. This requires establishment of pan-European grades on basis of the Bologna architecture utilising the ECTS system,
- Development of regional Centres of Reference serving as Clusters and co-ordination of activities within a European sub-region,
- Development of pharmaceutical medicine as a specific discipline of medicine,
- Identify finances available to set up new courses and training facilities,
- Establish courses so stakeholders easily could be able to obtain a basic knowledge on the whole R&D process including understanding of relevant regulatory guidelines,
- Provide training for people working in the field but not originally trained in the field. These accounts both for people changing their profile within a company (manager/project leader) or to a new area of expertise. Further to provide training to external stakeholders entering the field e.g. journalists,

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[37] Suggested stakeholders are: Industry and SMEs, Relevant/involved learned societies, Patients and/or consumers, Academia, through well-defined Europe-wide accepted bodies (e.g. Faculties organisations etc), Relevant Professional Organisations

[38] EU support could stimulate this process e.g. by support to highly qualified scientists to write textbooks in English to facilitate distribution of knowledge within Europe

- Constant identification and update of new scientific and technology developments and rapid implementation of corresponding training courses - Assessment of current availability of expertise in new and emerging fields of technology (e.g. toxicogenomics and other 'omics), combinatorial chemistry, systems biology, nanobiotechnology etc) across the EU,
- Increase mobility between academia industry and regulatory bodies, in a triangular way,
- Establish rapidly accessible mobility awards to allow pan-European access to courses and training facilities - Interaction with Marie-Curie units at the European Commission,
- Systematic postdoctoral E&T and financing thereof. Generation of a pan-European lifelong learning initiative related to Medicines Research including a credits system for professionals in the context of "continuous education" and update of original degree.
- Create standardised quality measures to be used for accreditation and evaluation of courses and to guarantee sustainability. Expand the model across the different levels of education.

5.5 Implementation plan and resources

Establishment of the pan-European platform for education and training is not done overnight. Careful mapping of existing activities within E&T including identification of European centres of excellence that can act as drivers and role models for other institutions and regions in Europe is needed. Many proposals have come up during the consultation process with stakeholders. Based on the mapping these proposals should be fleshed out with detailed implementation plans including evaluation of potential specific PhD grants. The activities appear from the table below.

1st priority is to establish a central coordinating unit.

2nd priority is to establish an advisory E&T council.

3rd priority is to establish a programme for integrated medicines development and for ethics committees and patient organisations.

4th priority is to establish programmes for safety sciences and scientists within pharmaceutical R&D

The programmes (3rd and 4th priority) are proposed to be established in 4 regions of Europe and courses are to be held twice a year.

Within the first year mapping to identify existing courses to populate figure 20 is a primary activity. Also planning of the specific programmes below together with a number of parallel activities is done. Eight major critical areas have been identified where there is a specific need for courses to support both current need and foreseen changes to the medicines R&D process.

PhD programme:

To facilitate interaction between academia and industry and to ensure that researchers to gain insight into the business related aspects of research and development, it is recommended to establish of 20 PhD grants for each of the 8 areas listed in the table below, i.e. 160 PhD grants. This programme should involve the co-operation of a university, a PhD fellow and an enterprise in a defined research and development project. Two supervisors will guide the Industrial PhD fellow, one from the university and one from the enterprise. The Industrial PhD fellow is employed by the company on a full time basis and paid for the entire period. The salary for the PhD student could be split as a public-private partnership where 50% is paid by EC/Marie Curie Action programme and 50% by the enterprise in question. To facilitate participation from SMEs, a proportion of these PhD should be fully financed by the EC.

The remaining priorities appear from the table below. Details on the activities and the budget are described in the report from the workshop 20-May-2005[39]. Where cost is indicated as "0" this is included in the running cost of the coordinating unit. The costs of the recommendations are estimates and will be subject to further analysis as appropriate.

[39] Workshop reports are posted on the Innovative Medicines website, http://europa.eu.int/comm/research/fp6/p1/innovative-medicines/index_en.html

	Duration	Responsible	Cost (€)
Short term budget			
Establish central coordinating unit, hiring personnel	3 months	Consortium	20'000
Running central coordinating unit 1 year including the following specific activities	12 months	Head of unit	297'000
Establish a council with representation of stakeholders	2 months	Head of unit	0
Meetings with the council, one every 3 months, 20 participants	12 months	Head of unit	90'800
1. Integrated medicines development, mapping and implementation plan (Priority score 10/10) Two meetings with relevant stakeholders (10 participants)	6 months	Head of unit	22'700
2. Ethics committee and patient organisation programmes, mapping and implementation plan (Priority score 10/10) Two meetings with relevant stakeholders (10 participants)	6 months	Head of unit	22'700
3. Safety science programmes, mapping and implementation plan (Priority score 9/10) Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
4. Scientists within pharmaceutical R&D, mapping and implementation plan (Priority score 9/10) Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
5. Pharmaceutical medicine, mapping and implementation plan (Priority score 9/10) Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
6. Regulatory affairs based programmes, mapping and implementation plan (Priority score 8/10) Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
7. Bio-statisticians, mapping and implementation plan (Priority score 7/10) Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
8. Bioinformaticians and biomedical informaticians, mapping and implementation plan (Priority score 7/10) Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
Parallel activities			
Establish criteria for what a centre of excellence in education is, to qualify the centre as a partner in a pan-European platform for education and training One meeting with relevant stakeholders (10 participants)	6 months	Head of unit	11'350

Explore the option for universities and higher education institutions to open their courses to participants from industry and to utilise industry competence in the faculty	6 months	Head of unit	0
Revisit the evaluation process of academicians considering also industrial experience. Currently, most often only the number of publications in high quality journals is taken into account for applicants to academic positions Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
Open dialogue with EU member states on curricula	12 months	Head of unit	0
Establish European criteria for curricula. Although the ECTS system and the Bologna process will result in broader comparability of degrees, especially for PhD courses there is no pan-European quality system. Some universities already ask for a given number of publications and/or patents. This should be standardised throughout Europe[40] Two meetings with relevant stakeholders (10 participants)	12 months	Head of unit	22'700
Explore an incentive system with the EU wide recognition and support to facilitate mobility of people from /to academia and industry	12 months	Head of unit	0
Explore development of an appropriate quality assurance / accreditation system	12 months	Head of unit	0
Map existing PPP in PhD training, e.g. graduate schools of research	12 months	Head of unit	0
Total short term budget			**646'150**

Long term budget for establishment of the E&T platform is pending mapping activities as mentioned above and detailed implementation plans. The following is therefore a rough estimation for a 6-year period.

Activity	**Costs (mio €)**
Running central coordinating unit for 6 years	1.8
For each of the following programmes the estimate is based on 2 courses per annum of 1 month duration for 26 participants in 4 regions of Europe	
1. Integrated Medicines Development	3.2
2. Ethics committee and patient organisation programmes	3.2
3. Safety science programmes 4.1 Development of a new curriculum 4.2 Courses	 0.5 3.2
4. Scientists within pharmaceutical R&D	3.2
5. Pharmaceutical Medicine	3.2
6. Regulatory affairs based programmes	3.2

[40] The Zagreb Declaration 2004 on harmonisation of PhD programmes in Medicine and Health Sciences, http://bio.mef.hr/conference/docs/Zagreb_Declaration_UK.htm

7. Bio-statisticians	3.2
8. Bioinformaticians and biomedical informaticians	3.2
160 PhD grants, 20 PhDs for each of the 8 areas (€ 150,000 each)	24.0
Total long term budget	**51.9**

Note: The long term budget includes the total cost for training programmes not taking into account that course fees may be paid by (some of the) participants. This would be feasible for some of the courses but not for e.g. ethics committee members and representatives from patient organisations. Further the extent of co-financing via public private partnership is not accounted for.

Key success factors

- Support from all relevant stakeholders, especially the European biomedical Industry, academia, learned societies, patient groups, regulatory bodies and the European Commission,
- Minimum bureaucracy to allow maximum flexibility and rapid action,
- As some of the activities are building on the progress of the Bologna process, the progress of this will be closely followed via the conferences in 2005, 2007 and 2009 and the result by 2010.

Performance measures

For a permanent control of the progress and performance the following measures and criteria might be applied:

- Number of attendances at courses and qualifications achieved,
- Number of trainees employed in biomedical industry and related fields,
- Number of students coming to Europe from abroad, especially from the USA,
- Development of curricula accepted by the scientific community,
- Acceptance and familiarisation of qualifications by universities, the scientific community, employers and regulatory bodies,
- Increased understanding of the needs and problems the biomedical industry has in regulatory, governmental and public bodies,
- Better informed public and patient groups,
- Increased investment in EU biomedical (long term success measure),
- Raised level towards innovation.

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6 Implementation

To successfully implement this SRA and establish collaborations between the different partners requires availability of resources, efficient management of these resources and adequate intellectual property rules. Discussions about these topics are currently ongoing between stakeholders and this chapter presents our initial thoughts. A more detailed proposal will be available in the next few months following additional analysis and consultation.

6.1 Organisation

The creation of an independent legal structure is under consideration to manage stakeholders' participation and to organise the operational aspects of the Innovative Medicines Initiative. That structure must be organised in the most efficient manner to maintain, fund and implement the Strategic Research Agenda. The general principles and ideas for this structure are presented in figure 21.

The basic concept is for the stakeholder forum to establish a non-profit organisation in order to implement the Innovative Medicines Initiative. The non-profit organisation will have a secretariat funded equally by the European Commission and EFPIA.

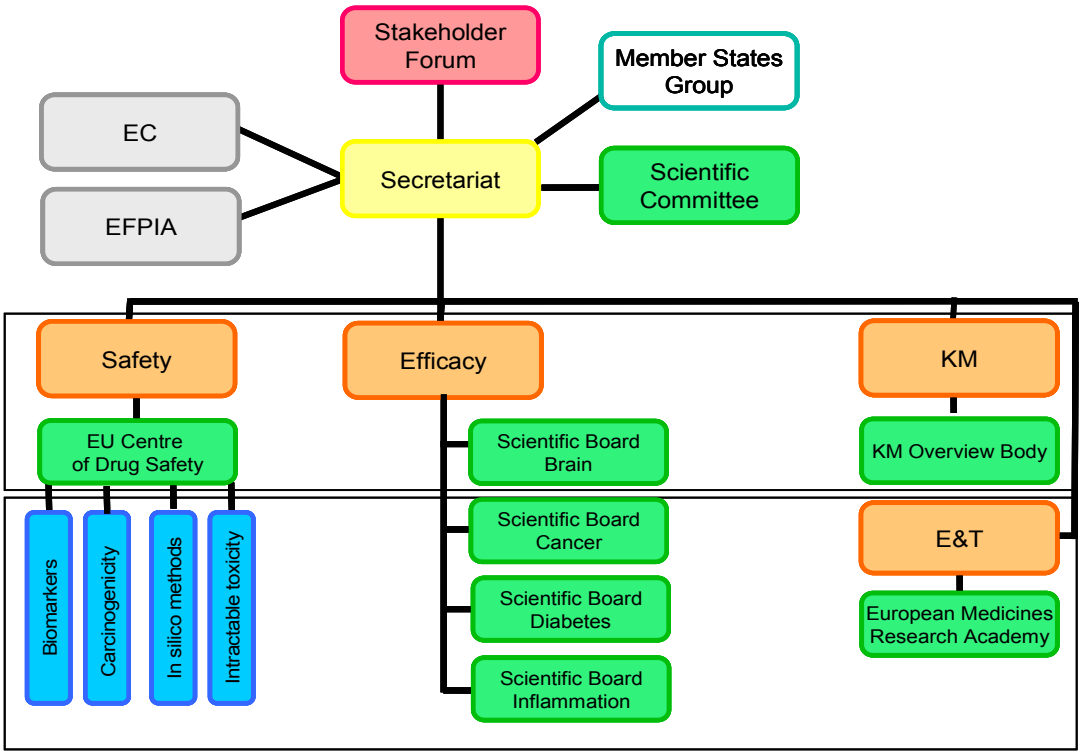

Figure 21: Proposed implementation structure

6.2 Roles and responsibilities within the organisation

The Stakeholder Forum

- Consists of representatives of the relevant stakeholders such as academia, charities, clinicians, European institutions, health departments, industry (including SMEs), patients organisations, research councils, regulatory agencies, etc.
- Responsible for oversight of the overall performance of the initiative as established by mutual agreement.
- Provides input to the Scientific Committee and aligns the stakeholders to the research priorities.

The Scientific Committee

- Advisory committee responsible for the Strategic Research Agenda (SRA), its updates, prioritisations and advising on proposals.

The Funding Members are the European Commission and the EFPIA.

- Makes funding decisions and ensures that contractual agreements are followed.

The Secretariat

- Has the operational responsibility for the implementation of the SRA and is responsible for day to day management.
- Has the responsibility to manage the portfolio of research projects.

The Member States Group

- Advisory committee and ensures alignment with national research programmes, and of the implementation of certain aspects of the SRA (i.e. education & training), will be involved in the nomination of the scientific committee.

6.3 Intellectual property rights

The objective of the general intellectual property (IP) policy for the Innovative Medicines Initiative is to achieve a large participation in the initiative and a fair allocation of rights on generated IP in case of commercial exploitation. Participation of biopharmaceutical companies and academic groups would be encouraged through easy access to a large amount of data and generated IP for research purposes. In addition, a fair allocation of rights helps to ensure that generated IP with a commercial potential is exploited diligently.

Initial principles for the patent and licensing policy are listed below:

- The right to the invention belongs to the inventor or to the legal entity according to the contractual relationship between the inventor and the respective legal entity,
- Use of these rights for research purposes, including clinical trials: free,
- Use of these rights for commercial purposes:
    - Free for anybody who has participated in the specific project in which the respective rights have been generated,
    - In case of non-participation in the specific project but participation in the Innovative Medicines Initiative: certain payments and/or royalty rate,
    - In case of non-participation in the Innovative Medicines Initiative: increased payments and/or royalty rate,
    - Participation is defined by financial investment up to a certain level or provision of certain data and/or tools/materials or undertakings determined/defined by the funding organisations.

A task force composed of representatives from the industry and from the European Commission will be established to further elaborate the principles of the general IP policy. The specific IP and Publication policy will be approved by the funding organisations.

6.4 Estimated costs

For each section of the Strategic Research Agenda, costs of the recommendations have been estimated and are summarized below; all figures are expressed in million euros per year. The duration of most of the research topics proposed varies between 5 and 7 years.

The total costs for the implementation of this SRA are estimated at **440 million euros per year**.

Figure 22: Estimated annual costs of implementation of the SRA

Improve Predictivity of Safety Evaluation, Clinical Safety and Pharmacovigilance	
Recommendations	Costs (mio €)
Create and run the European Centre of Drug Safety (42 FTEs)	15.4
Establish a framework for biomarker development	22.5
Study the relevance of rodent non-genotoxic carcinogens	22.5
Develop *in silico* methods	7.5
Tackle intractable toxicity	7.5
Other research projects to be defined	15.0
Clinical Safety and Pharmacovigilance	60.0
IT Infrastructure support	15.0
Total (million euros per year)	**165.4**
Improve Predictivity of Efficacy Evaluation	
Recommendations	Costs (mio €)
Cancer	66.7
Brain disorders	62.3
Inflammation diseases	60.0
Diabetes mellitus	37.7
IT infrastructure support	21.0
Total (million euros per year)	**247.7**
Improved Knowledge Management for Better Decision Making	
Recommendations	Costs (mio €)
Infrastructure, operations, licenses	10.3
Research projects	2.8
Total (million euros per year)	**13.1**
Improve Education & Training to Develop the Talent Base	
Recommendations	Costs (mio €)
Create and run European Medicines Research Academy (3 FTEs)	0.35
Running of training programmes	3.8
PhD grants	4.0
Total (million euros per year)	**8.2**

Implementation structure	
Recommendations	Costs (mio €)
Create and run the independent legal structure (about 20 FTEs for the secretariat)	6.0
Total (million euros per year)	**6.0**

6.5 Funding

In 2004, the pharmaceutical industry invested about 21.5 billion euros in R&D in Europe. This amount consisted of:

- 6.9 billions euros for discovery and pre-clinical development,
- 1.5 billions euros for phase I clinical trials,
- 2.4 billions euros for phase II clinical trials and,
- 10.7 billions euros for phase III clinical trials, regulatory approval and Pharmacovigilance.

In the context of the Innovative Medicines Initiative (IMI), it is foreseen that research performed by public organisations would be founded by the EC, while industry will contribute in kind. An overview of the proposed model for funding is given in the table below.

Stakeholder	**Contribution**	**How**
European Commission	Funding of the secretariat Funding of research	Contract between EC and secretariat and EFPIA and secretariat (50% each)
EFPIA	Funding of the secretariat	Contract between EC and secretariat and EFPIA and secretariat (50% each)
Pharmaceutical companies	Research Data Infrastructure Expertise	Funding via companies
Academia	Research Data Infrastructure Expertise	Funding via IMI
SME	Research Data Expertise	Funding via IMI and loans from European Investment Bank
Patients groups	Disease knowledge	Funding via IMI

Figure 23: Proposed funding principles

6.6 Participation

The scientific committee will define parameters or criteria for ensuring the successful implementation of the Strategic Research Agenda. Within these parameters, all stakeholders are welcome to propose how they could contribute to the implementation. It is foreseen that contribution to the implementation of the Strategic Research Agenda will be done through research collaborations between public and private institutions.

It is foreseen that the secretariat will publish calls for proposals as defined by the scientific committee, who will have the responsibility for evaluating the project proposals based on scientific excellence; clear rules will be established to ensure objectivity, transparency, etc.

The stakeholder forum will allow for the representation of the various stakeholder groups. The biomedical community is characterized by fragmentation, and it is important to establish how to best ensure adequate representation while ensuring the agility to act and make decisions, this will be explored and analyzed further in the second half of 2005.

7 Appendices

7.1 Report from Barcelona stakeholders workshop, April 2005

Sixth Framework Programme

LIFE SCIENCES, GENOMICS AND BIOTECHNOLOGY FOR HEALTH

To

Workshop Delegates and

DG Research, EU Commission

Summary Outcomes Report

Workshop on "How to Establish a European Technology Platform for Innovative Medicines", April 21-22, 2005, Barceló Hotel Sants, Barcelona, Spain.

The preliminary summary report has two objectives:

1) *To provide workshop delegates with an overview of the Innovative Medicines Initiative, its purpose and potential functions. It could also provide a basis for future work on national levels and in professional settings.*

2) *To present recommendations and conclusions from the workshop.*

A full report on the outcome of the workshop will be issued in July 2005.

Background

A European Technology Platform is a concept introduced by the European Commission to:

- Bring together all interested parties in a particular sector. The sector should be chosen for its strategic importance to contribute towards the EU's goals of knowledge-based growth, competitiveness and employment
- Foster effective public-private partnerships and bring together key stakeholders, under
- the leadership of industry, around a shared vision for the development of the technologies concerned
- Define the necessary research and technical priorities in the medium-long term for the sector.

A number of technology platforms are envisaged to receive funding via the Commission's Seventh Framework Programme (FP7).

To drive this forward for the biopharmaceutical sector, the European Commission asked the European Federation of Pharmaceutical Industries and Associations' (EFPIA) to identify the main barriers to innovation in biomedical research with the objective of establishing a European Technology Platform for Innovative Medicines, the Innovative Medicines Initiative, to tackle these.

The overall objective of the Technology Platform is the accelerated development of safe and efficacious medicines, aiming to bring tangible benefits to patients and revitalize the European biopharmaceutical research environment by strengthening the European science base.

The goals of the European Technology Platform for Innovative Medicines are:

- To better use the collective strength of the stakeholders of drug development through co- ordination and co-operation
- To better exploit existing European assets through collaboration
- To improve the drug development process via improved prediction of Efficacy and
- Safety, underpinned by Knowledge Management and Education and Training
- To create a new spirit and enthusiasm for European Drug research.

The objectives of the Barcelona workshop were:

- To provide further input to the work on the four parts of the Strategic Research Agenda, Safety, Efficacy, Knowledge Management and Education and Training
- To discuss ideas on how the implementation of the SRA could be effectively organised to attract stakeholders and achieve sustainability
- To activate relevant European stakeholders buy in to the Innovative Medicines Initiative.

Day 1

The first day was dedicated to understanding the process and content of the ongoing work on the Strategic Research Agenda. It was kicked off by presentations of the Technology Platform concept by Octavi Quintana-Trias, Director of DG Research and the Strategic Research Agenda by Jonathan Knowles, Chair of EFPIA's Research Directors Group. The work stream leaders for the four parts of the Strategic Research Agenda, presented the recommendations for Knowledge Management, Efficacy, Safety, and Education and Training, This was followed by breakout sessions, summaries are given below.

A1: Knowledge Management, chaired by Nicolas Grandjean, Novartis, Basel, CH

This session was dedicated to knowledge management issues within the context of Innovative Medicines Initiative. The main objectives are the development of an integrated collaborative environment, the definition of a common and flexible platform for federating data, resources and computing services, and the provision of knowledge management support to the Safety and Efficacy work packages. Efforts are done on the definition of relevant logical data layers, and on the development of powerful data resources, applications and services. Discussions during this workshop were focussed on the particularities and potentialities of the data resources. Current datasets should be annotated and curated for optimal relevance. An appropriate design of the future datasets would overcome current limitations. An inventory of current initiatives on biomedical datasets, representation models and specialised applications should be carried out. An integrated biomedical informatics perspective (from molecules and pathways to phenotypic data, incorporating interdisciplinary expertise) was considered crucial for the progress in the understanding of disease and drug mechanisms.

A2: Efficacy, chaired by Ian Ragan, Eli Lilly, Surrey UK

The session provided an opportunity to discuss the Innomed strategy on efficacy, which has the goal of improving clinical performance and early access to innovative medicine. This will initially be addressed in four areas; cancer, brain, diabetes and inflammation, each of these priorities illustrating specific bottlenecks in drug development

The discussion pointed to the need to merge national disease-oriented research programmes and networks in the corresponding fields. It emphasized the need to build on the European added value in drug development; quality of case records, quality of databases and biobanks, allowing further investigation of the

clinical features and biomarkers predicting the response to treatment. Active participation of patients and adaptation of regulatory procedures was discussed. The participants agreed that the planned research and development is important, and debated the scope of the non-competitive areas, and the relevance of the four priorities selected. An important point was the definition of competitive vs. pre-competitive fields as this may differ for big pharma, SMEs and academia.

A3: Safety, chaired by Friedlieb Pfannkuch, F. Hoffmann La Roche, Basel, CH

The chair presented the three priority topics for the Safety part of the Strategic Research Agenda for the Innovative Medicines Initiative

1. Framework for biomarker development & *in sili*co methods
2. Relevance of non-genotoxic carcinogens and other intractable toxicities
3. 'Virtual' European Office of Toxicology

The participants debated all three items intensely. They felt that it would be necessary to create a governance structure (The "Virtual" EU Office would be ideal), which will then have to prioritize and manage individual projects such as under priority topics 1 & 2 above. It was agreed that the relevance of non-genotoxic carcinogens and other intractable toxicities, is both important and relevant and would indeed impact positively the European scientific environment, the participants made specific recommendations on how to proceed with implementation.

A4: Education and Training, chaired by Jørgen Dirach, Novo Nordisk, Bagsværd, DK

The discussion group on Education and Training initially discussed issues leading to key statements pertaining to the content and objectives of Education versus Training, as well as to the identification of gaps and weaknesses in Education and Training. Specific issues were identified related to barriers, coordination, flexibility, quality and mobility. Consequently, objectives, key success factors, performance measures, quality management criteria as well as major criteria and characteristics for stakeholders to be on an Education and Training Council were defined. Universities should remain the centers for InnoMed related Education and Training but have to increase flexibility within their curricula and open their courses to participants from industry and utilize industry competence in the faculty. I was discussed if private vendors also could be considered to provide adequate quality. Since universities are currently changing their curricula to fit to the Bologna architecture there was a consensus that academia should be providing the bases for productive training by offering advanced courses on emerging disciplines and technologies. It was widely accepted that Marie-Curie type chairs should be provisioned for industrial people returning to academia and agreed that a central co- ordinating body with expert sub-groups to assess the availability and quality of training in preclinical, clinical and integrated drug development should be considered.

Day 2

The second day of the workshop was devoted to presentations and discussions on future stakeholder involvement in the Technology Platform, to bring forward strengths and weaknesses in a bottom up process, along with opportunities and threats that different groups are facing. This functioned as input on how to contribute to improving European competitiveness and strengthening the EU science base. A summary of these presentations can be found in Appendix.

The presentations were followed by breakout sessions, which are summarised below.

B1+B2: Issues on the establishment, attractiveness, organisation, functionalities and sustainability of the Platform, chaired by Ole J. Bjerrum, Danish University of Pharmaceutical Sciences, Copenhagen DK, and Jordi Cami, Institut Municipal d'Investigació Mèdica, Barcelona ES.

An organisational structure for the implementation of the Strategic Research Agenda is one way of securing the roll out of the proposed R&D. Such a structure must serve the objectives of the Strategic Research Agenda and its four parts. For these objectives to be successfully achieved the right stakeholders must be interested and participate actively, thus the structure should be organised to be attractive and accessible for potential relevant participants. In this context it is crucial that participation in projects is based on quality criteria. The complexity of the drug development process involves numerous skill sets across various stakeholder groups. For these to collaborate at European level any implementation structure must

be transparent and clearly organised. Involving organisations representing stakeholders at the European level will facilitate the establishment of such an implementation structure. The session proposed the following major European clusters of stakeholders involved in the drug development process. Universities and Research centres, Pharmaceutical Industry, Small and Medium size Enterprises SME, Regulatory and Quality authorities, Investors and, last, but not least, Patients.. For some of these stakeholders the representatives are already structured at European level (e.g. EFPIA, EMEA, EDQM, EIB, EIF, EPF). The participants also proposed for EU Networks of Excellence to be present.

Should a separate structure be used to implement the SRA, it should have clear and transparent rules for decision-making. An Executive Platform Committee could make decision with consultation of a European stakeholder forum. A scientific board should be involved with the implementation of efficacy, safety, knowledge management and training and education.

Such a structure may have a stable core with a programme plan that envisages funding for the duration of FP7 and potentially beyond. The participants were in favour of the concept of a public-private partnership support as a means for financing the platform.

B3: How to build on existing strength of the stakeholders to better exploit existing assets and resources and create values for industry and SME's, chaired by Jacques Demotes, ECRIN, CIC INSERM, Bordeaux FR.

Existing assets and resources in Europe include a high number of scientific publications from academia, a high level of technology in health systems and clinical research, and a growing innovative SME sector. Furthermore the regulatory agencies are open to discussion, and patients' organisations are willing to be an active partner. However, when discussing how to better exploit these European strengths, several levels of fragmentation appeared as bottlenecks to an efficient partnership: Translational gap between preclinical and clinical steps, insufficient networking at the EU level for basic research, and even more for clinical research and for patient's associations and cohorts; insufficient co-operation between industry, academia and patients. The participants' main conclusion was that networking and European integration is critical in building on European strengths and to improve the European science base. The industry needs academic networks to improve efficiency in preclinical and clinical development. Various pilot models for such networking were discussed, both for biotechnology development and for clinical evaluation.

B4: Post graduate training, chaired by Heidi Foth, University of Halle, Halle, DE

An important limitation in academic training that had been identified is that practical skills are vanishing from the curricula of universities as a result of general structural changes, which had been started in almost all countries of Europe. On the other hand, the boundaries between disciplines are vague in term of basic research at molecular levels. The urgent need to strengthen applied sciences is emphasised, because academic training is focussing too early in academic life and the skills of general awareness are vanishing (if not already been lost) in broad areas of research.

Concerning safety science issues, the need for specific postgraduate training activities in toxicology was taken up years ago and postgraduate training programmes were established in several countries in Europe. The existing experience shows that a multidisciplinary or interdisciplinary context can be established only on the basis of core scientific disciplines of individuals. The contents of courses must be thoroughly planned on basic, intermediate and specialised levels. The outcome of postgraduate training must be acceptable by industry, regulatory bodies and academia as well and for this certifications are needed. Participants should be trained to develop a balanced opinion. They will have to identify and handle conflicts between data or conflicts between hypotheses and practical experience.

Excellence in postgraduate training is a matter of contents and of a sound balance between new matters and established knowledge, which can rarely rely on the skills of individuals or individual institutions. Excellence in postgraduate training is also a matter of long-term activity and it cannot develop a reliable strength within normal time lines of a scientific projects. A critical success factor for such activities is that they be established in a fashion, which is independent from a turn over within professional staff. This can only be guaranteed if the driving force is taken up by a strong liaison between academia, professional bodies, industry and regulatory bodies.

B5: University research and education, incl. the forming of collaboration between basic and clinical research, chaired by Daan J A Crommelin, University of Utrecht NL

The session reached consensus that it would be valuable for a Pan–European initiative to set up training programmes in Drug Development at Universities and European Diplomas should be installed if training is expected to increase the overall EU competitiveness in drug development]. General issues debated included:

- Interdisciplinary training activities;
- The need to identify regional initiatives and European 'best practices';
- Student levels at which training should be provided as well as multiple entrance possibilities;
- Flexibility of training programmes and performance evaluation.

Training requirements for animal experimentation was emphasised. Further considerations included the predictability of the demand for training, for the needs of trainees and the existence of courses in the drug development area to serve as starting point. The participants agreed to propose an evolutionary approach that could start quickly by adjusting existing MSc and post- graduate training programmes and gradually broaden the offerings with new modules. High quality courses in Safety Sciences, as well as related PhD studies could be offer by centres of excellence. Nevertheless, too early specialisation should be avoided. A task force to determine the programme content was highly recommended.

Conclusions

There was general agreement throughout the workshop that implementing the European Technology Platform for innovative Medicines is an important component in re-establishing Europe as the primary location for biopharmaceutical research and development. The stakeholders acknowledged the value of industry leadership, the importance of the four topics of the Strategic Research Agenda, and the pre-competitive approach. The disease areas selected are appropriate for urgent research and do not reflect priority diseases of the FP7 life science programme.

Education and Training is a critical component of the Strategic Research Agenda. The strengths to support pharmaceutical industry needs do exist, however, fragmentation on a European level, including lack of collaboration between universities and higher education institutions hinders a coherent and coordinated approach. This highlighted the need for a pan-European organisation of academic institutions engaging in drug development. This, along with the lack of sufficient dialogue between the stakeholders of the drug development process, represents an important hurdle for efficient collaboration. If properly organised the Platform may contribute to remedy this gap.

All stakeholders play an important role in drug development, but as their respective SWOT analyses demonstrated, there are weaknesses to be addressed. Supportive functions of the Platform may optimise the stakeholder contributions, thereby securing more efficient use of the stakeholders' existing European strengths.

For academia the weakness concerns lack of critical mass of research groups, scientist and student mobility, new technologies, trans-disciplinary issues and positive public perception. A pan-European drug development organisation is highly needed to exploit the existing European strengths of the sector.

The clinical sector's contribution to European competitiveness can build on the quality of clinical research infrastructures, capacity of investigation, databases and biobanks, allowing to best exploit biomarkers and clinical data as predictors for safety or efficacy. In addition, the industry needs Europe-wide networks to make clinical research more efficient – infrastructure networks that provide harmonised tools and practice in Europe, research networks encompassing preclinical and clinical research, investigators' networks and patients' registries that facilitate enrolment.

For SMEs weaknesses include inefficient technology transfer from basic research, lack of management expertise, and holistically educated developers, as well as lack of existing accessible biology facilities, GMP units and toxicology databases.

For regulatory more research, conducted at the agencies, was recommended, e.g. by compilation of relevant generic data from old application files, openness to modern methodologies and technologies and reorientation of the regulatory assessment demands.

Learned societies which already organise scientists from academia, industry and the regulatory field, have a long tradition, based on a discipline-oriented European structure. They will, however, need to create a European organisation, which covers the complete drug developmentprocess. They could contribute by participating in a number of the coordination functions needed for and on the forthcoming platform.

Active involvement of patients and patients association's will promote drug development in line with patient's needs, foster their enrolment in studies, and the implementation of new treatment strategies.

Suggestions for better exploitation of existing assets and resources included more harmonisation (e.g. in clinical trials), EU-wide networking of biology facilities, GMP units, toxicology databases, and infrastructures and mobility.

There seemed to be general agreement that an "Executive Platform Committee" could be an appropriate leadership forum, but it was emphasised that the stakeholders should have a voice and consultative role through their European organisations. Various Technical offices, virtual and real, will have to be established.

Sustainability of the platform activities represents a critical issue, which was not addressed in depth. This should be further investigated.

Finally it should be noted that besides the described Technology Platform activities, the FP7 will provide its "normal" collaborative funding of life sciences research according to specific calls.

Participation

A total of 134 delegates from 21 countries accepted the invitation to and joined the 1½ days Workshop, on April 21-22, 2005, in Barcelona, 1/3 representing industry (19 from big pharma and 31 from SMEs), 1/3 academia and the remaining 1/3 the European Commission (8), regulatory agencies (5) and additional organisations (22), respectively. The female ratio was 1 to 5.

Postscript

The successful implementation of the European Technology Platform on Innovative Medicines, and thereby the strengthening of European competitiveness, will depend on the engagement of the stakeholders. Even though the Technology Platform has not yet been officially adopted for the 7th Framework Programme for Research and Technological Development, the concept is progressing with high Commission priority. Why not prepare yourself and your organisation for the final outcome.

Copenhagen, May 27, 2005

Ole J. Bjerrum, EUFEPS (Workshop Chair and Report Editor) Jacques Demotes, ECRIN

Andriani Odysseos, University of Cyprus

Ferran Sanz, EFMC Jurg Seiler, EUROTOX

Karen Strandgaard, EFPIA

Appendix 1. Summary keywords of the SWOT analysis given by the stakeholders invited to the workshop on How to establish a European Technology Platform for Innovative Medicines, on April 21-22, 2005.

Academia (Daan Crommelin)

Strength	Weaknesses	Opportunities	Threats
The European academic research in the field of pharmaceutical sciences has a **strong presence**. These groups develop new concepts and can **successfully compete** with leading groups in the USA/Canada and Japan/Korea/Taiwan. These fields of pharmaceutical science have a number of **internationally highly visible scientists**, who act globally as leaders in the field. The conclusion above is based on the observations of the high numbers of pub- lications/citations in the leading journals in the field of pharmaceutical sciences and the presence of the many academi- cians in the international Editorial Boards/Advisory Boards.	**Budget constraints** and rising personnel/consumables costs. **Exchange of persons** and goods within EU is problematic, and it is even more difficult to attract gifted young scientists from countries outside the EU. The public perception of and the **position of science/scientists**, in general, has 'eroded' over the years. This has given rise to increasingly strict legislation regarding animal- and clinical testing and to the strong adversary attitude regarding the introduction of molecular biological find- ings in the public domain. **Critical mass** for running successfully innovating research groups only is existing in a relatively small number of centres. That means: • scattering in sub-critical mass facilities • research activities often lack focus • leading to lack of depth and no (inter)national visibility and recognition. **New technologies** from molecular biology, biotechnology and material sciences only slowly find their way to European academic groups in the pharmaceutical sciences. The advantages of **transdisciplinary** research activities are broadly recognized but the implementation is still a point of concern. The tradition to build up an **intellectual property** portfolio and to license out patents is poorly developed.	**Initiatives** by European organizations such as EUFEPS (New Safe Medicines Faster) give the field of pharmaceutical sciences new chances. Networks (e.g. EU Galenos network and BioSim) also help. Identification of key fields of interest. European organizations or new not yet formed e.g. Drug Science Forum should identify key fields of interest in the phar- maceutical sciences and a program should be initiated to build **European focus groups/centres** with critical mass and research focus to stimulate internal coherence and synergy as well as for expensive infrastructure (e.g. for upscaling research). Blockades against the free '**flow' of scientists** and goods should be removed Pan-European **training courses** in the pharmaceutical sciences in the English language. The efforts to combine **pan-European conferences** on Pharmaceutical science (cf. 'PharmSciFair in Nice 2005') should be stepped up. Increased awareness of **intellectual property** rights where policies should be further developed at universities as part of the Ph.D. training program. Spin-off activities should be promoted as well by introducing liberal conditions and early 'entrepreneurial training for scien- tists.	Emerging economies, such as India and China. Moving pharmaceutical industry. The pharmaceutical industry is consolidating and the trend is to move to the USA for economic reasons. As the pharmaceutical industry has been and should be a strong supporter of academic research, this 'moving out' undermines academic research. Leadership. The field of pharmaceutical sciences needs European champions but they are few and the next generation are not cultured.

Appendix 1. Summary keywords of the SWOT analysis given by stakeholders invited to the workshop on How to establish a European Technology Platform for Innovative Medicines, on April 21-22, 2005.

Clinical Sector (Josep Torrent-Farnell)

Strength	Weaknesses	Opportunities	Threats
• Regarding professional stimuli and recognition of the clinician who: • • Is highly motivated for very innovative medicines • Networks with outstanding worldwide colleagues • Publish interesting clinical trials in leading medical journals • Becomes through specialization in one area: "Opinion Leader" • Is highly recognised by patients, families and media • May develop new clinical research paradigms, particularly new methodolo- gies and statistical approaches for rare diseases and emerging therapies • -Growing experience in partnering and leading multi-professional research team Increasing understanding and participation on drug-research regulatory demands • -Foster new patients-doctors relationship frames	Regarding input of "true" medical needs the clinicians increasingly: • Become passive by "performing the trial" with limited contribution to the protocol or to the outcomes • Get "invited" to collaborate in industry on less motivating project (e.g. me-to-drugs) • Lack support of the health institution: • "Your priority is not our priority" • Difficulties in getting appropriated funding for the functioning of the Research Team • Lack of public funding for the conduct of Independent (non-industry sponsored) Clinical Investigations • Scarce technical facilities to full-fill with all GCP's administrative burdens	Further consolidation of research capacities through: • Continuing medical education and training • Fast exchange of relevant information with other partners • Collaboration and competition to stimulate "Excellence" • Improved knowledge-based medicine practice • Recognition as "experts" by the regulatory bodies (avoiding potential conflict of interests) • A more proactive role to give input to industry projects • Empowerment for conducting independent non-industry sponsored clinical research • Better understanding of patients needs and health priorities • Consolidation of the research capacities of the group and center • Improving patient care and management based on experience gained from research	Undermining of the medical responsibilities and doctor-patients relationship by: • Being reduced as a provider of "clinical data" only (i.e. outsourcing / supply relationship vs partnering) • Higher standards in clinical research activities compared to conventional medical care • Being overwhelmed by product-driven activities instead of disease-oriented clinical research • Losing credibility and patient's trust by neglecting individual patients needs • Shortage of high-level independent experts for regulatory assessments with no conflict of interest • Vulnerability of the Research Team by failing in consolidating its medium-long- term sustainability

Appendix 1. Summary keywords of the SWOT given by analysis stakeholders invited to the workshop on How to establish a European Technology Platform for Innovative Medicines, on April 21-22, 2005.

Small and Medium sized Enterprises (Axel Mescheder)

Strength	Weaknesses	Opportunities	Threats
Biotech has delivered about 190 approved medicines which accounts for 20% of all drugs currently on the market.	Financing the downturn in the financial markets weakens the sector.	Success will be achieved if:	Transmission - „Gap“
Trend continues with several hundreds of biotech products in clinical development throughout the world accounting for 50% of all new medicines in development.	Strong patent protection is essential and is not alvays present.	Strong financial muscles, clear product focus and appropriate regulatory and reimbursement strategy are provided.	Inefficient Technology-Transfer from basic research, lack of foundation matur- ity and lack of management experience.
Biotech companies generated more than $46 billion in revenues globally in 2003. European Biotechnologies deliveries were in 2003 about 250 new products in the pipeline of public companies and almost 70 Phase III – compounds in trials of European public companies.	Cost of drug development is increasing, with huge data requirements for quality, safety and efficacy.	“Drying pipeline” to be filled by biotech collaboration. Thus half of 25 biotech drugs approved by FDA in 2003 were bio- tech-big pharma co-operations. Further- more 383 reported co-operations in 2003 – globally steadily increasing.	Financing - „Gap“
Key therapeutic areas addressed ex- pressed as % of products in development: Cancer - 40%, infectious diseases - 11% and autoimmune & neurological disor- ders 5%	A significant volume of successful launches in Europe has yet to get off the ground.	Strategic alliances continue to be the life blood of the biotech industry.	Unfledged venture capital Industry, lack of federal and EC-funding, lack of alter- native investors. Too few Investments in early stage projects.
EU Biotech growth faster than US.	Strategic alliances continue to be the life blood of the biotech industry.	200 Biotech-pharma alliances in 2003 (47% Europe-Europe, 45% Europe-US and10% Europe-others).	Partnering - „Gap“
		Liaison with government to ensure that patient access to innovative treatments continues to be effective.	Early stage products and lack of win-win partnerships. Pharm-Risk adversity.
			Products to Market - „Gap“
			Anything that hampers investors incentives where the key elements are: • Will the product get to market by own sales force or by marketing partnership. • A robust, predictable regulatory approval system. A regulatory system matching scientific progress. • A financial market environment which allows the development of innovative medicine. • Existence of alliances with Pharmaceutical companies on win-win basis.

Appendix 1. Summary keywords of the SWOT analysis given by the stakeholders invited to the workshop on How to establish a European Technology Platform for Innovative Medicines, on April 21-22, 2005.

Learned Societies (Christian Noe)

Strength	Weaknesses	Opportunities	Threats
Learned Societies can • be the spearhead on the Platform for Innovative Medicines. • harmonise research in different phases and fields of Drug Discovery and Development. • Contribute to early identification of emerging topics and new techniques in drug discovery. • organise themselves into a European drug development network (Drug Science Forum). • play a pivotal role in organisation of Education and Training as they house Academia, Industry and Regulatory. European Learned Society exists for most disciplines of drug R&D. They organise researchers discipline wise, and at the same time house academia, industry and regulatory and have an ef- fective infrastructure for their members. They can take initiatives fast and move quickly. Money allocated for their organisation will increase their output immediately. With independent scientific and social commitment they represent a third force not exploited earlier.	Lectures, symposia and training courses become increasingly commercial activities, frequently competing with traditional activities of Learned Societies. Learned Societies are dependent from the money flow between industry, acade- mia via conferences, journals and courses. The money flow should not be drained to private vendors. New media (Internet, data bases) are a big help to Learned Societies, but may result in an “overkill” of information. The expanding ”event society” may render some social activities of Learned Societies old fashioned.	Learned Societies may • transfer Promising Science Related Activities from the Local to the Regional and European Level. • promote Cooperation and Common Scientific and Educational Programmes of European Universities. • support Exchange of Scientists. Above all by building a European ”post-doc” Market. • support Intraeuropean Mobility of Researchers and Professionals. • integrate Organisations vertically (local to European) and horizontally (different disciplines). That the professional, social and ethical commitment of scientists and decision makers involved in the discussion of the platform will initiate a process that will convince everybody to join forces to create a powerful European Technology Platform for Innovative Medicines.	Marginalisation by not being professional enough due to lack of investments in building a modern infrastructure (Office, secretarial assistance, communication). If the main driving force is the wish to get significant EU money for oneself the European Technology Platform for Innovative Medicines will be biased and not be sufficiently strong for global competition. A unique chance to proceed towards a globally competitive European Drug Research Community would be lost.

Appendix 1. Summary keywords of the SWOT analysis given by the stakeholders invited to the workshop on How to establish a European Technology Platform for Innovative Medicines, on April 21-22, 2005.

Patient involvement (Yann Le Cam)

With the purpose to achieve the quickest access to as many safe, efficient and affordable innovative medicines for all patients in Europe

Strength	Weaknesses	Opportunities	Threats
The strength of the patients is as "Experts of experience" for their disease. They have knowledge of patient needs and a high level of collective conscience based on individual and collective empowerment. They may participate in research projects (as leaders or partners) and they have growing experience in clinical trials (ex: HIV/AIDS, cancer, rare diseases/orphan drugs).. The patients show increasing participation to the regulatory process (regarding COMP, Protocol Assistance, Risk Management). Patients are being increasingly better organised in groups and networks. Further they train patient representatives in clinical research, information and networking with a good outreach (local, regional, national, European, International)	European associations (cross-diseases and/or cross-national organizations, forums, alliances) are less than 10 years old. Lack of financial resources and sustainability. Lack of human resources (e.g. patient representatives speaking English and being "collective" and "educated" on clinical research) and being lack of time (e.g. most patients groups are only run by volunteers, management of job and diseases).	The patient's organisations may • be supportive of research and medical progress. • facilitate patient recruitment. • develop communities of patients. • create trust by patients and families. • create trust by society. • get growing influence. • partner with all stakeholders. • collaborate with Industry when in an open and fair manner • change relationship between doctors and patients to be more informed, empowered and pro-active. The key success factors are: • full involvement in InnoMed governing bodies. • good practices in relationship between sponsors and patient organisations (e.g. Charter). • transparency; consistency between com- munication and action. • address public health needs where society calls for it: tangible benefits perceived by patients. • accept time line for mutual learning process. • accept long term learning curves to build capacities. • empower patients groups through training and information and accept constructive confrontation.	Risk of loosing independence: Vulnerability to sources of funding. Potential instrumentalisation by industry and/or by authorities Miss perception of risk by individual patients. "Zero risk" mirage society/policy mak- ers/media. Excessive professionalism and institu- tionalisation of patient representation.

7.2 The use of animal in research and development – EFPIA Policy statement

Introduction

EFPIA represents the research-based pharmaceutical industry of twenty-five European countries. Its members, between them, have saved and improved the quality of life for millions of people. EFPIA member companies are committed to the alleviation of suffering caused by currently untreatable or inadequately treated medical conditions, bringing new, safe and effective therapies to patients.

The process that leads to the development of a new medicine is long and complex and involves a range of different research methods. Research in animals is an essential part of that process, providing vital information that scientists and doctors need to decide if a medicine should go on to be tested in people.

EFPIA members recognise the importance of animal welfare and strive to ensure that the number of animals used in research is kept to the absolute minimum necessary to obtain the required information. They are committed to avoid or minimise the distress or pain of animals and to always treat them with compassion and respect. Non-animal methods are used wherever it is scientifically possible and where the law and regulatory authorities allow it.

Most of the effects of medicines that cannot currently be seen using non-animal methods can be predicted from well-designed animal studies. To go into human testing without the benefit of this information would expose people to unacceptable risk. It would also be illegal. With good reason, regulators around the world demand evidence from animal studies before they will permit clinical trials to be conducted.

Why animals?

When body systems work together they create new conditions that do not exist in cell culture and cannot be fully replicated on computer. The effects (both wanted and unwanted) of a medicine will ultimately depend on what happens when a medicine interacts with all the body's systems. Even after extensive testing in the "test tube" or in cellular systems, a compound may have a dramatically different effect in the whole body – for example liver metabolism may change the structure of the molecule, the molecule may collect in the kidney or, through a very indirect route, may affect blood pressure.

As our biological knowledge increases, so too does the usefulness of non-animal methods. There is however, a long way to go. There are still enormous gaps in our biological knowledge that limit the usefulness of cell culture and computer based research. The computer that could simulate the entire workings of the brain, let alone the interaction with the heart, liver and kidney, has yet to be invented.

Well-designed animal studies will remain essential to bridge the gap between test tubes and people for the foreseeable future. The biological similarity between ourselves and other animals, together with good understanding of the differences in the biology of the various laboratory animal species, means that most of the potential effects of a medicine in the human body can be predicted from such studies.

Progress in alternatives

EFPIA fully supports the concept of the '3Rs' and its member companies constantly put them into practice. These principles include: **R**eplacement (i.e. to substitute animals with valid non-animal techniques), **R**eduction (i.e. to use methods that allow the necessary information to be obtained from fewer animals) and **R**efinement (i.e. to use methods which cause the least possible distress).

EFPIA strongly encourages scientifically sound research to reduce the need for animals. In fact, the pharmaceutical industry has been at the forefront of developments that have led to big reductions in the number of animals needed in some areas.

EFPIA has also been a major driver in the International Committee on Harmonisation (ICH) since its creation in 1990. ICH was formed to agree common testing standards and requirements, including protocols involving animals, among the medicines regulatory agencies of the US, EU and Japan. Without such agreement, pharmaceutical companies can be forced to repeat tests, using slightly varying protocols, to satisfy individual national regulatory requirements. The work of the ICH has led to worldwide reductions in the number of animals needed in certain areas.

At the same time, our increasing biological understanding is opening up new areas of research, bringing hope for the future for people living with, and often dying from, many intractable conditions. This means that animals are being used in areas of research that hardly existed before. While every effort should be made to reduce the number of animals used in research, it would be unethical to do so at the expense of human health and well-being.

EFPIA PRINCIPLES OF ANIMAL WELFARE

Researchers and the research organisations they work for have a moral (and legal) responsibility to treat the animals with care and compassion before, during and after the research. The principles of laboratory animal welfare promoted by EFPIA are set out below:

1. Compliance with the EC Directive 86/609, the Council of Europe Convention ETS 123 and appropriate national laws governing the use of animals in research;
2. Responsibility at all times for the humane care and a compassionate approach to laboratory animals before, during and after experimental procedures;
3. The conduct of research involving animals on the basis of sound and well-defined scientific objectives and carefully controlled conditions to ensure that research does not have to be repeated.
4. Provision of properly trained and competent staff to care for the animals and to carry out experimental procedures;
5. The conduct of procedures in a way which causes the least possible distress and pain to the animals;
6. Provision of appropriate and adequate facilities for the housing and transport of all laboratory animals;
7. The choice of the most appropriate method based on sound science, in order to obtain the required information that will ensure that a potential new medicine or vaccine can proceed to further testing in man for efficacy and safety reasons.
8. The use of non-animal methods wherever they can realistically provide the required information;
9. Development of reliable and validated research methods that reduce the need for animals:
10. Promotion and encouragement for progress in developing experimental techniques which will lead to the replacement and/or reduction of tests on animals and/or the refinement of methods;
11. Support for European and international initiatives which further the above without impeding pharmaceutical research and other medical progress (e.g. International Conference on Harmonization [ICH] and the activities of the European Centre for Validation of Alternative Methods [ECVAM]);

Efpia 1998, Revised: September 2004

7.3 Epidemiology data on inflammatory diseases

Osteoarthritis current and future estimated prevalence by country, 2003 and 2010			
	2003	**2010**	**CAGR (%)**
US (000s) 1,3	26,060	29,466	1.8
US (% of population)	9.2	9.9	
Japan (000s) 1,2	15,935	17,924	1.7
Japan (% of population)	12.5	14.1	
France (000s) 1	5,804	6,356	1.3
France (% of population)	9.7	10.5	
Germany (000s) 1	8,596	9,600	1.6
Germany (% of population)	10.4	11.7	
Italy (000s) 1	6,248	6,808	1.2
Italy (% of population)	11	12.2	
Spain (000s) 4	4,780	5,270	1.4
Spain (% of population)	12.1	13.1	
UK (000s) 5	5,810	6,303	1.2
UK (% of population)	9.8	10.6	
Total	**73,233**	**81,727**	**1.6**

1. Lawrence RC *et al.* (1998), Felson DT *et al.* (1987 and 1995) Lanes SF *et al.* (1997), Bolen J *et al*. (2002).
2. Yoshida S *et al.* (2002)
3. Hochberg *et al.* (1995) and RCGP 1991 Morbidity stats from General Practice and applied to US data.
4. Carmona L *et al.* (2001)
5. Felson *et al.* (1998)
Stakeholder Insight: Osteoarthritis Survey (Q1.5) used to extrapolate total OA prevalence from studies on a single joint.

Rheumatoid Arthritis population, main five Europe, by age and sex, 2003					
	RA population by age (000s)				
	15–44	**45–59**	**60–74**	**75+**	**Total**
France male	1.3	17.7	21.4	18.4	58.8
France female	8.4	57.9	62.3	50.9	179.6
France total	9.7	75.5	83.7	69.4	238.4
Germany male	3.5	47.7	73.0	42.0	166.2
Germany female	19.8	134.5	184.3	126.6	465.2
Germany total	23.3	182.2	257.3	168.6	631.4
Italy male	1.0	13.8	20.5	16.3	51.6
Italy female	6.1	42.7	56.6	41.4	146.8
Italy total	7.1	56.5	77.1	57.7	198.4
Spain male	0.7	8.5	12.0	10.2	31.4
Spain female	7.0	42.0	52.7	39.7	141.3
Spain total	7.7	50.4	64.7	49.9	172.7
UK male	2.4	33.7	44.1	36.8	117.0
UK female	14.2	97.7	108.2	86.4	306.5
UK total	16.6	131.4	152.3	123.2	423.4
Main 5 EU male	9.0	121.3	171.0	123.7	424.9
Main 5 EU female	55.5	374.8	464.0	345.1	1,239.4
Main 5 EU total	**64.5**	**496.1**	**635.0**	**468.7**	**1,664.3**

Source: Symmons et al, 2002 (UK); Saraux et al, 1999 (France); Cimmino et al, 1998 (Italy); Carmona et al, 2001 (Spain), UN Population Database, 2003

TRA prevalence, main five Europe, 2003						
	France	**Germany**	**Italy**	**Spain**	**UK**	**Total**
% of population, 15+	0.49%	0.90%	0.40%	0.51%	0.88%	0.67%

Source: Symmons et al, 2002 (UK); Saraux et al, 1999 (France); Cimmino et al, 1998 (Italy); Carmona et al, 2001 (Spain), UN Population Database, 2003;

Asthma prevalence and diagnosed population by country and age, 2005								
	US	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**Average**
Prevalence (%)								
Children (0–14)	7.9	5.7	6.1	7.1	6.0	4.8	13.7	7.3
Adults (15–64)	7.2	3.6	4.6	4.4	3.6	4.0	7.9	5.0
Elderly (65+)	8.7	5.1	6.1	5.9	5.1	5.5	9.4	6.5
Average	7.9	4.8	5.6	5.8	4.9	4.8	10.3	6.3
Population (m)*	**US**	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**Total**
Children (0–14)	63.6	17.9	11.2	11.9	8.0	5.8	10.7	129.1
Adults (15–64)	199.6	84.9	39.6	55.3	38.1	28.3	39.4	485.2
Elderly (65+)	36.9	25.2	9.9	15.4	11.2	7.1	9.5	115.2
Total	300	127.9	60.7	82.6	57.3	41.2	59.6	729.3
Asthma population (m)	**US**	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**Total**
Children (0–14)	5.0	1.0	0.7	0.8	0.5	0.3	1.5	9.5
Adults (15–64)	14.4	3.1	1.8	2.4	1.4	1.1	3.1	24.5
Elderly (65+)	3.2	1.3	0.6	0.9	0.6	0.4	0.9	7.5
Total	22.6	5.4	3.1	4.2	2.4	1.8	5.5	41.5
Diagnosed population (m)	**US**	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**	**Total**
Children (0–14)	3.4	0.7	0.5	0.6	0.3	0.2	1.0	6.7
Adults (15–64)	12.1	2.6	1.5	2.0	1.2	1.0	2.6	22.9
Elderly (65+)	1.6	0.6	0.3	0.5	0.3	0.2	0.4	3.9
Total	17.1	3.9	2.3	3.1	1.8	1.3	4.1	33.5
** UN database figures*								
Source: DMHC2046								

COPD prevalence and diagnosed population by country and disease severity, 2005								
	US	**France**	**Germany**	**Italy**	**Spain**	**UK**	**Japan**	**Total**
Population* (m)	300.0	60.7	82.6	57.3	41.2	59.6	127.0	728.4
Prevalence (%)	4.1	4.4	4.6	4.6	4.4	4.3	4.4	
Segment size (m)	12.3	2.7	3.8	2.6	1.8	2.6	5.6	31.4
Mild (31%)	3.8	0.8	1.2	0.8	0.6	0.8	1.7	9.7

Moderate (35%)	4.3	0.9	1.3	0.9	0.6	0.9	2.0	11.0
Severe (34%)	4.2	0.9	1.3	0.9	0.6	0.9	1.9	10.7
Diagnosed population (m)								
Moderate (~0%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Moderate (~50%)	2.2	0.5	0.7	0.5	0.3	0.5	1.0	5.5
Severe (~90%)	3.8	0.8	1.2	0.8	0.6	0.8	1.7	9.6
Total diagnosed population (m)	**5.9**	**1.3**	**1.8**	**1.3**	**0.9**	**1.3**	**2.7**	**15.1**
* UN database figures								
Source: DMHC1615								

Allergic rhinitis prevalence and population by country, 2005

	US	**France**	**Germany**	**Italy**	**Spain**	**UK**	**Japan**	**Total**
Population (m)	300.0	60.7	82.6	57.3	41.2	59.6	127.0	728.4
Prevalence (%)	19.8	24.6	18.2	17.1	14	26.5	19.6	n/a
Allergic rhinitis population (m)	**59.4**	**14.9**	**15**	**9.8**	**5.8**	**15.8**	**25.1**	**145.8**
** UN database figures*								
Source: DMHC1936								

Prevalence and incidence of CD by country

Country	**Population, 000s**	**Prevalence per 100,000**	**Prevalence**	**Annual incidence per 100,000**	**Annual incidence**
US	293,028	144.1	422,253	5.8	16,996
Japan	127,333	5.85	7,449	0.51	649
France	60,424	30.7	18,550	9.2	5,559
Germany	82,425	30.7	25,304	4.4	3,627
Italy	58,057	40.0	23,223	2.5-4.4	2,555
Spain	40,281	19.8	7,976	5.1-5.2	2,095
UK	60,271	75.8	45,685	3.8	2,290

Totals	**721,819**	**N/a**	**550,441**	**N/a**	**33,770**

US: Loftus EV Jr *et al.,* Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gastroenterology*. 1998 Jun; 114 (6): 1161-1168. Erratum in: Loftus EV Jr, Reply. *Gastroenterology*. 1999 Jun; 116 (6): 1507.

Japan: Morita N *et al*., Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. *Journal of Gastroenterology*. 1995 Nov; 30 Suppl 8: 1-4.

France: prevalence: German prevalence applied to French population; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). Gut. 1996 Nov; 39 (5): 690-697.

Germany: prevalence: Gastro-Pro; incidence: Shivananda S et al., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut*. 1996 Nov; 39 (5): 690-697.

Italy: prevalence: Trallori G et al., A population-based study of inflammatory bowel disease in Florence over 15 years (1978-92). *Scandinavian Journal of Gastroenterology*. 1996 Sep; 31 (9): 892-899; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996 Nov; 39 (5): 690-697.

Spain: prevalence: Gastro-Pro; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996 Nov; 39 (5): 690-697.

UK: prevalence: Gastro-Pro; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996 Nov; 39 (5): 690-697.

Where range is given for incidence, higher estimate is used to calculate patient numbers

Totals may not tally due to rounding

na: not applicable

Prevalence and incidence of UC by country

Country	Population, 000s	Prevalence per 100,000	Prevalence	Annual incidence per 100,000	Annual incidence
US	293,028	229	671,034	7.6	22,270
Japan	127,333	18.12	23,073	1.95	2,483
France	60,424	27.3	16,496	6.7	4,048
Germany	82,425	27.3	22,502	4.1	3,379
Italy	58,057	121.0	70,249	8.6-9.1	5,283
Spain	40,281	109.96	44,293	7.4-9.8	3,948
UK	60,271	30-122	73,531	10	6,027
Totals	**721,819**	**N/a**	**921,177**	**N/a**	**47,439**

US: Loftus EV Jr *et al*., Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gut*. 2000 Mar; 46 (3): 336-343.

Japan: Morita N *et al*., Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. *Journal of Gastroenterology*. 1995 Nov; 30 Suppl 8: 1-4.

France: prevalence: German prevalence applied to French population; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996 Nov; 39 (5): 690-697.

Germany: prevalence: Dirks E *et al*., [Prospective study of the incidence and prevalence of ulcerative colitis in a large urban population in Germany (western Ruhr area)]. *Zeitschrift für Gastroenterologie*. 1994 Jun; 32 (6): 332-337; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996 Nov; 39 (5): 690-697.

Italy: prevalence: Trallori G *et al*., A population-based study of inflammatory bowel disease in Florence over 15 years (1978-92). *Scandinavian Journal of Gastroenterology*. 1996 Sep; 31 (9): 892-899; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut*. 1996 Nov; 39 (5): 690-697.

Spain: prevalence: Saro Gismera C *et al*., [Incidence and prevalence of inflammatory bowel disease. Asturian study in 5 areas (EIICEA). Spain]. *Anales de Medicina Interna*. 2003 Jan; 20 (1): 3-9; incidence: Shivananda S et al., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut*. 1996 Nov; 39 (5): 690-697.

UK: prevalence: Gastro-Pro; incidence: Shivananda S *et al*., Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut.* 1996 Nov; 39 (5): 690-697.

Where range is given for prevalence or incidence, higher estimate is used to calculate patient numbers

7.4 Inflammatory diseases detailed analysis

7.4.1 Osteoarthritis

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.	Biomechanical property evaluation tools.	The availability of biochemical evaluation tools and their relation to quality of life markers would enable to predict the impact of deterioration or improvement on the patients and better assessment of therapies.	specific	Under Validation	European orthopaedic research society, EULAR, Patient groups	Academia = industry > patients > Clinicians		Validated Accepted	
Develop better disease models (especially in-vivo), which are more predictive for drug efficacy.	Develop Clinical OA subtype specific animal models.	Development of subtype specific animal models of OA will allow to develop subtype specific therapies to be subsequently tested in clinical trials.	specific	Under Validation	EULAR; European Orthopaedic Research Society; Industry	Industry = Academia > Clinicians = Patients	8M€ over 5 year	Validated Accepted	No NIH initiatives

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Increased research into disease mechanisms to provide for true-disease modifying therapeutic opportunities as distinct from simple symptomatic treatment.	Genomic diagnostic, prognostic, outcome biomarkers.	Biochemical and Genomic biomarkers would identify the patient characteristics associated with early OA as well as those associated with more rapid progression of OA for the selection of patient populations for POM/POC trials.	specific	Under Validation	EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund	Clinicians = Patients = Academia > Industry	2000 pts; 20M€ over 5 year	Validated Accepted	US NIH Program (OAI) already initiated - read out 2005-2010 [This in not a program that will provide much information on disease mechanisms. Rather it will provide information on how a variety of indicators change over the 5 year period.
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new [4]therapies.	Joint function assessment tools.	Validated Joint function assessment tools would allow to determine quality of life and changes in quality of life within short term after initiation of therapy and improve the evaluation of response to therapy.	specific	Under Validation	EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund	Academia = Patients = Clinicians > Industry	Subsets of patients needed; total 5000 over 5 years; 6M€ over 5 years		
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	[5]Imaging biomarkers	A more sensitive and precise imaging biomarker could identify a compound early in development that significantly alters the rate of progression of OA through reduction of joint (e.g., cartilage) destruction.	OA & RA	Mature	EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund	Clinicians = Patients = Academia > Industry			US NIH OAI Project. The project does not contain any intervention.

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biochemical outcome, mechanism, diagnostic, prognostic biomarkers.	Biochemical and Genomic biomarkers that can identify early in development a compound capable of significantly altering the progression of OA would allow pursuit of a product concept that is cost-prohibitive with the available technology.	specific		EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund;	Clinicians = Patients = Academia > Industry	2000 pts; 25M€ over 7 year		
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.	Outcome research questionnaires. Specific outcome studies demonstrating reduction in time to joint replacement would be valuable.	QoL measures validated for OA would allow to identify patients with the highest need of therapeutic intervention and to assess response to therapy; they would also allow to discern the best BioImaging markers to be used as surrogates.	OA	Under Validation	EULAR; European Orthopaedic Research Society	Clinicians = Patients > Academia > Industry	3000 pts; 6M€ over 5 year		Competition in Canada; Australia; US
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Develop biochemical marker kits for in office physician use with following attributes (1) Easy access (2) Implementable in clinic, lab or home (3) Results can be interpreted by PCPs, rheumatologists & orthopaedic specialists to monitor efficacy.	This would allow early diagnosis and introduction of disease modifying intervention before major tissue damage has occurred.	OA	Under Validation	EULAR; Nordic Bioscience	Industry = SMEs > Academia > Clinicians = Patients	5000 pts; 15M€ over 5 year		

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

7.4.2 Rheumatoid Arthritis

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Imaging/Biochemical Diagnostic Biomarkers. To select patients with early disease.	This would allow initiation of early treatment to appropriate patients which could lead to prevention and delay of joint damage & disability and improvement in remission. Could also potentially identify novel targets.	RA	Under Validation	EULAR	Academia = Industry = SMEs > Clinicians = Patients	2000 pts; 30M€ over 5 year			Europe Leading Edge
Develop better disease models (especially in-vivo), which are more predictive for drug efficacy. [4]	Need models that reflect clinical chronicity & exacerbation pattern of RA.	Would allow for better drug targeting & validation. Models need to be validated through genomic comparison of key pathways in models and patients.	specific	Under Validation	EULAR; IP Autocure	Industry = Academia > Clinicians = Patients	12M€ over 5 year	Validated Accepted		

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome. [5]	Imaging/Biochemical Prognostic Biomarkers. To identify patients at risk for rapid progression to shorten clinical trials.	This would allow initiation of early treatment to appropriate patients which could lead to prevention and delay of joint damage & disability and improvement in remission. Could also potentially identify novel targets.	RA	Under Validation	EULAR	Academia = Industry = SMEs > Clinicians = Patients	2000 pts; 40M€ over 7 year			Europe Leading Edge
Increased research into disease mechanisms to provide for true-disease modifying therapeutic opportunities as distinct from simple symptomatic treatment.	Epidemiological studies to identify at risk populations; to select patients with early disease and to identify patients at risk for rapid progression to shorten clinical trials.	Better knowledge on disease mechanisms would allow the development of better targeted therapies; knowledge on subsets of disease would allow specific-tailored therapies to be developed and tested, including improved assessment of benefit: risk ratios	RA	Under Validation	National databases & EULAR	Clinicians = = Industry = Patients > Academia	30,000 pts; 20M€ over 7 year		Knowledge Management	Europe Leading Edge

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.	Prognostic Disability & Activity Scores.	New and better tools to address novel endpoints such as remission or to distinguish better between effects of different therapies would allow to better address the efficacy of novel targeted therapies and reduce trial sizes.	RA	Under Validation	EULAR	Clinicians = Industry = Patients > Academia	10,000 pts; 8M€ over 5 year		Knowledge Management	
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome. [6]	Develop biochemical marker kits for in office physician use.	Important for early disease detection, prognostication and early therapy.								

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome. [7]	Imaging Outcome Biomarker Joint ultrasonography. Sensitive for measuring synovial inflammation via detection of synovial thickening and synovial vascularity. Inexpensive. Prone to operator and reader bias, potential issues with reproducibility renders.	Use of novel biomarkers of disease progression would allow earlier recognition of treatment effects or failures and to reduce the length and the size of trials.	RA	Under Validation	EULAR	Academia = Patients > Clinicians > Industry	2000 patients; 20M€ over 5 years			
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	RA biomarker that correlates with clinical outcomes.	Availability of prognostic biomarkers would allow to subset patients for clinical trials and improve long-term outcome of disease by directing intensive therapies to such populations; this would also improve the benefit: risk ratio	RA	Under Validation	EULAR	Academia = Patients > Industry > Clinicians	4000 patients; 8M€ over 5 years			
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Safety biomarker for immunosuppressive side effects. This is a necessity in RA where physicians are uneasy with broad immunosuppresives.	Availability of biomarkers to predict safety of therapies would decrease adverse events and increase benefit: risk ratio	All diseases	Under Validation	All major European Societies	Industry > Academia = Patients > Clinicians				

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Prednisone Methods Study in humans: Identify inflammation and side effects biomarkers that are differentially modulated by prednisone.	Such biomarkers would allow to design "safe" glucocorticoids which are badly needed given their excellent therapeutic effects but having a significant adverse event profile.	All diseases	Under Validation		Industry > Academia = Patients > Clinicians				

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area

7.4.3 COPD

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs [4]	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarkers of lower airway inflammation.	Inflammation of the lower airways is a recognized as an important component of the pathophysiology of both severe asthma and COPD. Currently accepted measures of the effects of inflammation, such as lung function tests, are all indirect and not sufficient.	Specific	Under Validation	ERS	ATS-ERS Joint Task Force on COPD Biomarkers	Clinicians = Patients = Academia > Industry	2000 pts; 10M€ over 5 year	Validation Accepted	ERS-ATS workshop on biomarkers in COPD; SMEs.
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarker of disease progression.	The inflammation in the airways changes during COPD stages of disease. Current accepted measures do not reflect this.	specific	Under Validation	ERS		Clinicians = Patients = Academia > Industry	2000 pts; 5M€ over 5 year	Validation Accepted	

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area

[4] (eg hubs, imaging centers of execlence, patient DBs)

Priority Research Area	Enabler Description [1]	Rationale 2	Enabler Scope 3	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs 4	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Develop better disease models (especially in-vivo), which are more predictive for drug efficacy.	Model of lung destruction & physiology.	Further our knowledge of the pathways driving tissue inflammation & tissue destruction.	specific	Under Validation	Industry; SMEs; Academia		Industry = SMEs > Academia > Clinicians = Patients	10M€ over 5 year	Validation Accepted	US; Canada; Australia
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome. [5]	Airway Challenges/PFT	A model of neutrophilia that could allow for POM studies which targeted therapies.	specific	Under Validation	Academia; Clinicians		Clinicians = Patients = Academia > Industry	200 pts; 3M€ over 2 year	Validation Accepted	

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area

[4] (eg hubs, imaging centers of execlence, patient DBs)

7.4.4 COPD/Severe Asthma

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs [4]	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarkers in Exhaled Breath Condensate/sputum.	Non-invasive means of measuring airway inflammation & control. The HbA1C of asthma!!	specific	Under Validation	ERS; SMEs; Industry	EU Collaboration on Severe Asthma (BIOAire) & ATS-ERS Joint Task Force on COPD Biomarkers	Industry = SME = Academia > patient = Clinician	1000 pts; 2M€ over 2 year	Validation Accepted	ERS-ATS workshop on biomarkers in COPD; Nth American Investigators in collaboration with Industry.
Increased research into disease mechanisms to provide for true-disease modifying therapeutic opportunities as distinct from simple symptomatic treatment.	Genomic diagnostic, prognostic, outcome biomarkers.	Biochemical and Genomic biomarkers would identify the patient characteristics associated with early COPD and Severe Asthma as well as those associated with more rapid progression of disease for the selection of patient populations for clinical trials.	specific	Under Validation	ERS		Clinicians = Patients = Academia > Industry	2000 pts; 20M€ over 5 year	Validation Accepted	

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area

[4] (eg hubs, imaging centers of execlence, patient DBs)

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs [4]	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Develop better disease models (especially in-vivo), which are more predictive for drug efficacy. [5]	Model of exacerbations in controlled conditions.	Further our knowledge of the pathways driving exacerbations thus directing better therapies.	specific	Under Validation	ERS; SMEs; Industry; Academia		Industry = SMEs > Academia > Clinicians = Patients	7M€ over 5 year	Validation Accepted	
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.[6]	Better outcomes measure.	Current accepted measures of lung function in patients with moderate to severe airways disease are not sensitive to intervention and do not adequately reflect the well-being of patients. QoL measurement may be a more precise tool to monitor clinical outcome.	specific	Under Validation	ERS; BTS		Clinicians = Patients = Academia > Industry	2000 pts; 5M€ over 5 year	Validation Accepted	ATS
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarkers for lung damage and repair.	Damage & repair to the lung is recognized as an important component of the pathophysiology of both severe asthma and COPD. Currently accepted measures of the effects of inflammation, such as lung function tests, are all indirect and not sufficiently specific.	specific	Under Validation	ERS	ATS-ERS Joint Task Force on COPD Biomarkers	Clinicians = Patients = Academia > Industry	2000 pts; 10M€ over 5 year	Validation Accepted	ERS-ATS workshop on biomarkers in COPD; Nth American Investigators in collaboration with Industry.

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

[4.] (eg hubs, imaging centres of excellence, patient DBs)

7.4.5 Severe Asthma

Priority Research Area	Enabler Description [1]	Rationale [2]	Enabler Scope [3]	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs [4]	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Airway Challenges/PFT.	A functional measure that can diagnose sub-clinical disease; provide early POC.	specific	Under Validation	Academia; Clinicians		Clinicians = Patients = Academia > Industry	200 pts; 3M€ over 2 year	Validation Accepted	
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome. [5]	Biomarker of lower airway inflammation in Asthma.	Inflammation of the lower airways is a recognized as an important component of the pathophysiology of both asthma and COPD. Currently accepted measures of the effects of inflammation, such as lung function tests, are all indirect and not sufficiently specific.	specific	Under Validation	Academia; Clinicians; Industry; SMEs		Clinicians = Patients = Academia > Industry	2000 pts; 10M€ over 5 year	Validation Accepted	EU collaboration on severe asthma (BIOAire).

[1] (Outline of the scientific approach)

[2] (How does the efficacy enabler address the bottlenecks?)

[3] (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

[4] (eg hubs, imaging centres of excellence, patient DBs)