



**The Innovative Medicines Initiative (IMI)
Strategic Research Agenda**

*Creating Biomedical R&D Leadership for Europe
to Benefit Patients and Society*

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http://www.efpia.org/4_pos/SRA.pdf

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Executive Summary

The Innovative Medicines Initiative (IMI) is a unique pan-European public and private sector collaboration between large and small biopharmaceutical and healthcare companies, regulators, academia and patients. The aim of IMI is to support the faster discovery and development of better medicines for patients and enhance Europe's competitiveness by ensuring that its biopharmaceutical sector remains a dynamic high-technology sector. The Innovative Medicines Initiative will ensure that Europe's biomedical sciences receive targeted strategic support for the benefit of patients, as well as the scientists and citizens of Europe.

IMI proposes a number of clear, practical paths that will accelerate the discovery and development of more effective innovative medicines with fewer side-effects. IMI will implement innovative Patient Centred Projects that address the principle causes of delay or bottlenecks in the current biomedical R&D process. These bottlenecks have been identified as: predicting safety, predicting efficacy, bridging gaps in knowledge management and bridging gaps in education and training. The Strategic Research Agenda (SRA) describes the recommendations to address these bottlenecks and a plan to guide their implementation. These recommendations represent the outcome of an extensive consultation between Europe's key stakeholders in the biomedical sector. The Strategic Research Agenda is a 'living' document and will be up-dated based on scientific advances.

To implement the Innovative Medicines Initiative, the European Commission and the European Federation of Pharmaceutical Industries and Associations will hold joint responsibility for creating and operating a new non-profit international organisation. This organisation will have a legal mandate to award research grants to European Public-Private Collaborations conducting innovative research projects focused on implementing the recommendations of the SRA.

The SRA consists of recommendations across four strategic areas ('Four-Pillars') that address the principal causes of delay in the biomedical R&D process as summarised below:

- Predictivity of Safety Evaluation (Pillar I): Nine recommendations are presented. These include the creation of a European Centre of Drug Safety Research, and establishing a framework to develop biomarkers that will have human relevance and regulatory utility;
- Predictivity of Efficacy Evaluation (Pillar II): Five recommendations are presented related to each of the five disease areas that have been identified as priorities for Europe, based on unmet medical need. These recommendations include creating disease-specific European Imaging Networks, developing regional centres of excellence, creating disease-specific European centres for the validation of new biomarkers and enhancing collaborations with patients and regulatory authorities;
- Knowledge Management (Pillar III): Fifteen recommendations are presented. These include establishing a Translational Knowledge Management team to support Pillar I and Pillar II projects, and creating a Knowledge Management Platform to develop effective data integration and analysis tools;
- Education and Training (Pillar IV): Five recommendations are presented that include establishing a European Medicines Research Academy, and the implementation of multi-disciplinary programmes to develop skills in integrating biology and medicine expertise.

As part of the European Union's 7th Framework Programme, the Innovative Medicines Initiative will be proposed by the European Commission for Joint Technology Initiative status, subject to approval by Member States. To implement the recommendations of the Strategic Research Agenda fully will require an investment of about €460 million per year, or more than €3 billion across seven years starting in 2007. The European Commission and the biopharmaceutical companies will contribute equally towards this investment. The European Commission will fund academic participants in research collaborations, and support Small and Medium-Sized Enterprises, while the biopharmaceutical company participants in research collaborations will completely fund their own contributions to the Initiative.

Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society is the vision of this powerful partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations, who are supporting the Innovative Medicines Initiative with strategic and financial resources.

Table of Contents

1	Introduction	7
1.1	The Strategic Research Agenda	7
1.2	Stakeholder Involvement.....	12
1.3	Contributions to Standards.....	13
1.4	Impact of IMI on the Use of Animals in Research and Development	14
1.5	Key Benefits of IMI	15
1.6	The Biopharmaceutical Sector's Contribution to the Lisbon Agenda.....	15
1.7	R&D Performance	19
1.8	Signatures of the EFPIA Research Directors' Group Members.....	23
2	Improved Predictivity of Drug Safety Evaluation	24
2.1	Summary	24
2.2	Introduction.....	24
2.3	The European Centre of Drug Safety Research	27
2.4	Priority Areas for Research in Non-clinical Safety	30
2.5	Priority Areas for Research in Pharmacovigilance and Risk Management	33
2.6	Resources	35
2.7	List of Contributors	36
3	Improved Predictivity of Efficacy Evaluation	38
3.1	Summary	38
3.2	Introduction.....	38
3.3	Cancer	46
3.4	Brain Disorders.....	54
3.5	Inflammatory Diseases.....	60
3.6	Metabolic Diseases	70
3.7	Infectious Diseases	79
4	Knowledge Management	85
4.1	Summary	85
4.2	Introduction.....	86
4.3	Translational KM	88
4.4	The KM Platform	91
4.5	Resources	97
4.6	List of Contributors	99
5	Education and Training	100
5.1	Summary	100
5.2	Introduction.....	100
5.3	Gap analysis.....	101
5.4	Recommendations	103
5.5	Implementation Plan and Resources	106
5.6	List of Contributors	111
6	Governance and Funding	112
6.1	Legal Status	112
6.2	Structure.....	112
6.3	Funding	114
6.4	Overview of IMI Costs by Pillar	115
6.5	Overview of IMI Costs by Type	116
6.6	Communication	117
6.7	List of Contributors	118
7	Intellectual Property	119
7.1	Objectives and Principles.....	119
7.2	Intellectual Property Rights Policy.....	119

7.3	List of Contributors.....	122
8	Appendices	123
8.1	Consolidated List of Contributors in Alphabetical Order.....	123
8.2	The Use of Animal in Research and Development – EFPIA Policy Statement.....	133
8.3	Epidemiology Data on Inflammatory Diseases.....	135
8.4	Inflammatory Diseases Detailed Analysis.....	140
8.5	Glossary.....	150
8.6	Abbreviations Used.....	152

Table of Figures

Figure 1 : Reasons for Attrition	7
Figure 2 : Key Bottlenecks in the Pharmaceutical R&D Process	8
Figure 3 : Global R&D Expenditure, Development Times and NMEs 1995–2004	9
Figure 4 : Interdependencies between the Four-Pillars of the Strategic Research Agenda	10
Figure 5 : Stakeholder Analysis of Contributors to the SRA.....	12
Figure 6 : Trade Surplus of Europe's Biopharmaceutical Industry 2000–2005.....	15
Figure 7 : R&D Employees of Europe's Biopharmaceutical Industry 2004	16
Figure 8 : Global Biotechnology R&D Investment by Company Origin 2003–2005	17
Figure 9 : Comparison of R&D Intensity	17
Figure 10 : Comparison of R&D Intensity Growth	18
Figure 11 : Comparison of Government Support for R&D (GBAORD).....	18
Figure 12 : Health R&D in Government Budgets as a Percentage of GDP, 2002	19
Figure 13 : Examples of National Biomedical Research Funding in 2005	19
Figure 14 : Global NME Approvals 1986–2005.....	20
Figure 15 : FDA Oncology NME Approvals 2000–2005	20
Figure 16 : Regions of First Launches of NMEs 1998–2004.....	21
Figure 17 : Comparison of European and US Pharmaceutical R&D Expenditure 2000–2005	21
Figure 18 : Examples of Organisations Involved in the Drug Safety Evaluation Process	28
Figure 19 : Structure of the ECDSR and Interaction with Knowledge Management.....	28
Figure 20 : Minimal Biomarker Pre-Validation Prior to Acceptance	31
Figure 21 : Efficacy Issues are Often Disease Specific.....	39
Figure 22 : Potential Data Sharing Model.....	44
Figure 23 : Cancer Mortality in the EU15	47
Figure 24 : Incidence and Prevalence of Cancer Across EU Countries.....	48
Figure 25 : Brain Diseases Costs and Incidence.....	55
Figure 26 : Global Infectious Diseases Prevalence.....	79
Figure 27 : Positioning the IMI Knowledge Management.....	87
Figure 28 : Knowledge Management Embedding and Bridging	88
Figure 29 : Knowledge Management Functional Architecture.....	94
Figure 30 : Organisation of the E&T Platform.....	104
Figure 31 : Proposed IMI Implementation Structure.....	112
Figure 32 : IMI Funding Model.....	114
Figure 33 : IMI Funding Sources	114
Figure 34 : Estimated Annual Costs of Implementation of the SRA.....	115
Figure 35 : Distribution of the SRA Total Yearly Costs (€0.46 bn)	116
Figure 36 : SRA G&A Budget Cost Drivers	116

1 Introduction

The Innovative Medicines Initiative (IMI) is a unique pan-European public and private sector collaboration between large and small biopharmaceutical and healthcare companies, regulators, academia and patients. The aim of IMI is to support the faster discovery and development of better medicines for patients and enhance Europe's competitiveness by ensuring that its biopharmaceutical sector remains a dynamic high-technology sector. The Innovative Medicines Initiative will ensure that Europe's biopharmaceutical sector receives targeted strategic support for the benefit of patients, as well as the scientists and citizens of Europe.

IMI proposes a number of clear, practical paths that will accelerate the discovery and development of more effective innovative medicines with fewer side-effects. IMI will implement innovative Patient Centred Projects that address the principal causes of delay or bottlenecks in the current biomedical R&D process. These bottlenecks have been identified as predicting safety, predicting efficacy, bridging gaps in knowledge management and bridging gaps in education and training. The Strategic Research Agenda (SRA) describes the recommendations to address these bottlenecks and a plan to guide their implementation.

1.1 The Strategic Research Agenda

The bottlenecks were identified through extensive consultation with stakeholders in the biomedical R&D process and from the literature. For example, data on product attrition rates indicate that the probability of a drug candidate passing from pre-clinical stages (i.e. the first GLP toxicity study) to market is 6% or less³. The most common factors resulting in project failure have been reported as either a lack of efficacy (25%), clinical safety concerns (12%) and toxicological findings in pre-clinical evaluation (20%), as illustrated in Figure 1 below. Reducing the risks associated with project failure is dependent upon a concerted and collaborative effort to address these bottlenecks in the drug development process. The biopharmaceutical industry's greatest need is for failure to be predicted at the earliest possible stage of the drug development process. Advances in basic biomedical science within the entire European research community could, potentially, make a significant contribution to improving the predictability of the biomedical R&D process. The vision for the future would be to possess the ability to identify lack of efficacy as soon as possible, even when a drug has promising pre-clinical data, and the potential for adverse drug reactions and pre-clinical toxicity.

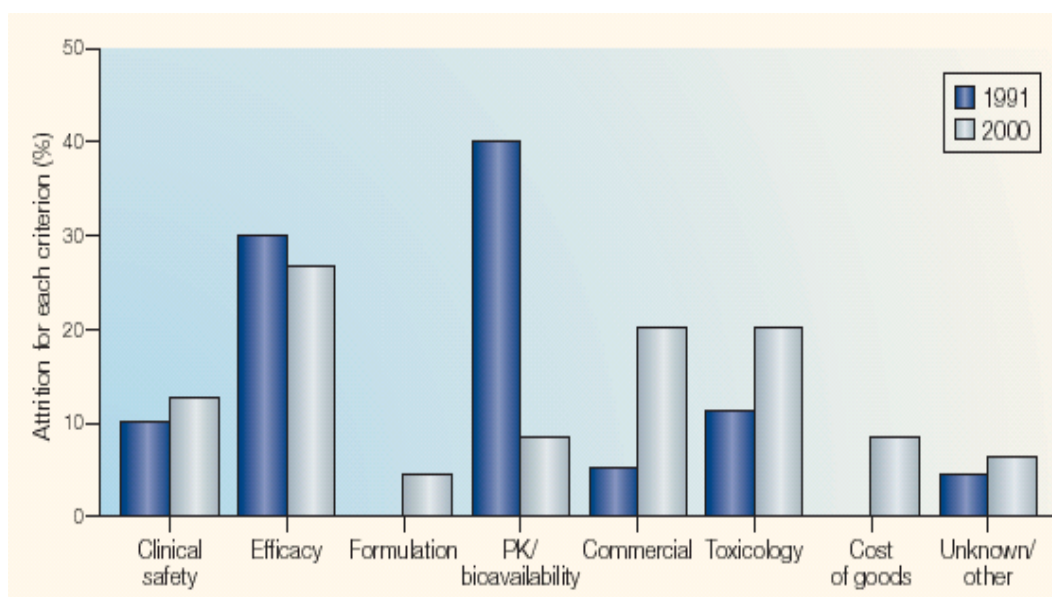


Figure 1 : Reasons for Attrition

The most significant advance in the drug development process between 1991 and 2000 was the optimisation of drug design through the improved predictive value of drug metabolism studies. This advance

³ Kola I and Landis J (2004). A Survey of Pharmaceutical Companies Comparing Reasons for Attrition. *Nature Reviews Drug Discovery*; 3: 711–715.

was possible because *in vitro* absorption and metabolism screens have been validated by correlation with clinical data. The Innovative Medicines Initiative aims to achieve similar clinical correlations within the different scientific disciplines described in Figure 1 above. It also aims to expand on the advances already made with the aforementioned *in vitro* screens through scientific synergies created by unique pan-European public and private sector collaborations. These collaborations conduct pre-competitive research projects, i.e. research where companies are not adverse to their competitors having equal access to the results. An example of a pre-competitive research project would be research that is aimed not at producing products, but rather at providing the: tools, information and data that enable all competing companies to develop and register future products and services.

As illustrated in Figure 2 below, the pre-competitive barriers or bottlenecks in the current biomedical R&D process are the predictivity of pre-clinical studies to anticipate clinical safety and clinical efficacy, as well as the overall assessment of patient benefits and risks with regulatory authorities. Regulatory processes need to reflect new knowledge and incorporate this new knowledge into an improved regulatory framework that supports the faster discovery and development of better medicines. This will increase patient access to new medicines, and decrease the escalating cost of drug discovery and development. Leveraging scientific and technological advances around these bottlenecks could, potentially, boost Europe's biomedical R&D base, and accelerate the discovery and development of better innovative medicines.

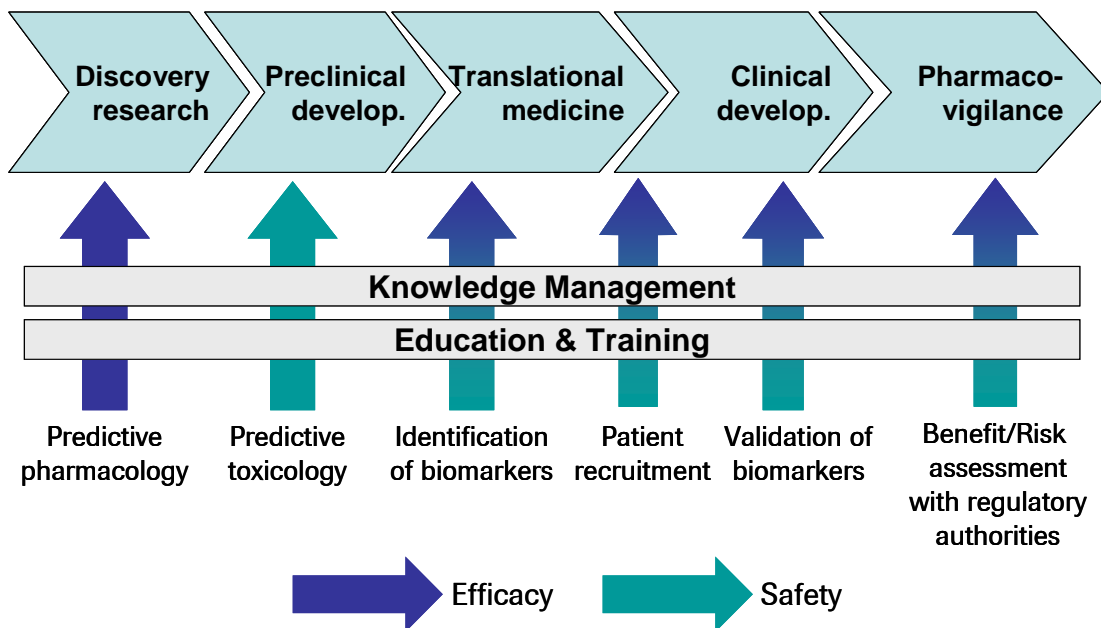


Figure 2 : Key Bottlenecks in the Pharmaceutical R&D Process

The Strategic Research Agenda addresses issues in all of the areas where pre-competitive bottlenecks exist, and proposes specific areas of research to improve the overall efficiency of medicine development in Europe. This is an ambitious aim, but one that is not considered to be beyond the collective capabilities of Europe's biomedical sector. The sector has recognised the urgent need to revolutionise the conventional drug development paradigm to support the faster discovery and development of better medicines.

The development of a new drug is a long, complex and resource-intensive process. Various estimates have placed the costs between \$400 mn and \$900 mn during the period 1994 to 2000⁴. There is a high possibility that a new drug will fail to reach the market because projects may fail for different reasons at different points in the overall process. During the previous 10 years, global R&D expenditure in the pharmaceuticals and biotechnology sector has steadily increased, without a corresponding increase in output of new medicines, as illustrated in Figure 3 below.

The data presented in Figure 1 and Figure 3 demonstrate that radically different initiatives are urgently needed to reduce the rate of attrition during the downstream phases of the drug discovery and development process. Such initiatives would support the faster discovery and development of better medicines, and provide a boost to Europe's biomedical R&D base. This would enable Europe to become a preferred

⁴ DiMasi JA, Hansen RW, Grabowski HG (2003). The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*; 22: 151–185.

location for biopharmaceutical industry investment. In recognition of this opportunity, the Research Directors Group of EFPIA has identified the pre-competitive barriers in the drug discovery and development process on which the biopharmaceutical industry, as well as other stakeholders in the biomedical R&D process such as academia, can collaborate.

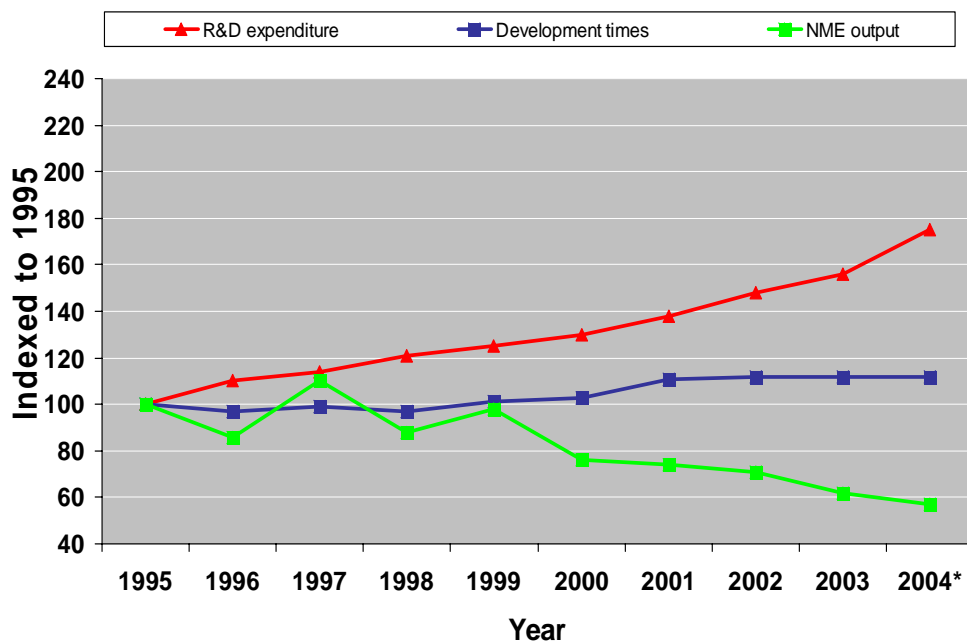


Figure 3 : Global R&D Expenditure, Development Times and NMEs 1995–2004⁵

The SRA includes recommendations that encompass the entire biomedical R&D process from discovery to launch and beyond i.e. pharmacovigilance. These recommendations address the bottlenecks in the conventional drug discovery and development process, and also include important regulatory considerations. To accelerate the discovery and development of more effective innovative medicines with fewer side-effects that reach patients faster, both the safety and efficacy evaluation of new molecular entities (NMEs) across the entire drug development process need to be improved, as well as knowledge management and education and training capabilities.

The SRA is organised around four strategic areas, or Four-Pillars, as described below:

- **Predictivity of Safety Evaluation (Pillar I):** This addresses bottlenecks related to predictivity in safety evaluation and benefit–risk assessment with regulatory authorities;
- **Predictivity of Efficacy Evaluation (Pillar II):** This addresses bottlenecks related to predictive pharmacology, the identification and validation of biomarkers, patient recruitment and benefit–risk assessment with regulatory authorities;
- **Knowledge Management (Pillar III):** This addresses bottlenecks related to gaps in information technology, providing platforms to analyse large amounts of information in an integrated and predictive way. This pillar will be key to maximising the potential of new platform technologies such as genomics, and in analysing data generated by IMI in a consistently integrated manner;
- **Education and Training (Pillar IV):** This addresses the bottlenecks related to gaps in expertise in biomedical R&D knowledge and skills. This pillar will identify and address specific gaps in knowledge and capabilities: a bottleneck which must be resolved if the safety and efficacy pillars of the SRA are to be supported effectively. The education and training pillar will also ensure that Europe’s biomedical education landscape is enhanced to provide maximum support in revolutionising the conventional drug discovery and development paradigm.

The strategy of IMI is to co-ordinate and leverage the joint public–private investment within each of the Four-Pillars of the SRA, thereby creating synergies between the new scientific knowledge and capabilities in each of them to support the faster discovery and development of better medicines. The interdependencies between the Four-Pillars of the SRA are illustrated in Figure 4 below.

⁵ Centre for Medicines Research International Ltd. CMR International 2005/2006 Pharmaceutical R&D Factbook (2005).

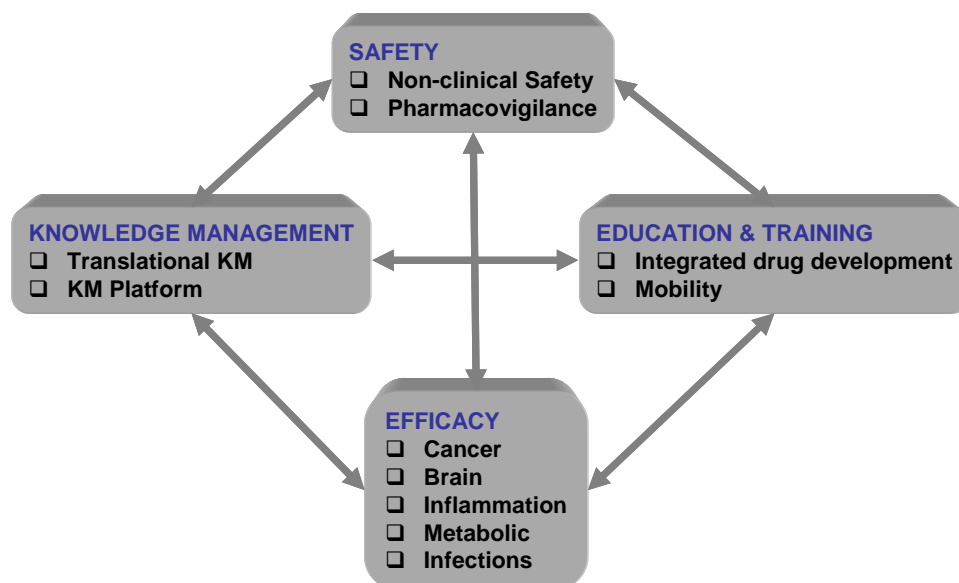


Figure 4 : Interdependencies between the Four-Pillars of the Strategic Research Agenda

Improved Predictivity of Safety Evaluation

To improve the predictivity of safety evaluation and address the current high attrition rate in drug development, the following nine recommendations have been agreed:

- Create a European Centre of Drug Safety Research (ECDSR) 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 animals for human risk;
- Optimise data resources and strengthen the evidence base in pharmacovigilance;
- Develop and strengthen methodologies and networks for pharmacovigilance;
- Develop novel methods of risk prediction and benefit–risk assessment;
- Train and educate health care professionals and patients.

Improved Predictivity of Efficacy Evaluation

To improve the predictivity of efficacy evaluation and to address the current high attrition rate in drug development, the following nine recommendations have been agreed:

- 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 to establish standards, ensure imaging biomarkers are validated, and develop regional centres of excellence;
- Create disease-specific European Centres for the validation of omics-based biomarkers;
- Co-ordinate the development of national patient networks and databases 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 the 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 the joint consideration of ethical issues.

Knowledge Management (KM)

To address the KM bottlenecks in discovering and developing new medicines, the following 15 key recommendations have been agreed:

- Set up a Translational KM team to support individual Safety and Efficacy projects, to define standards of compatibility across projects, and to promote the sharing of suitable KM technology;
- Set up a KM Platform team that, through partner consortium projects, conceives the overall architecture for an integrating biopharma / biomedical sciences platform;
- Set up an advisory Science Panel that supports the KM team in applied Information Technology matters, the ongoing evaluation of *prior art*, and the identification of complementary and synergistic technology R&D proposals;
- Set up task forces to evaluate cross-disciplinary aspects such as modelling and simulation of physio-pathological processes, validate specifications, and align priorities;
- Set up a cross-disciplinary task force to propose guidelines concerning non-KM issues related to data sharing, for example legal, regulatory, ethical and intellectual property;
- Evaluate the approaches and the investment required to build the core of a platform backbone ontology;
- 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, datasets, scientific objects, and data elements;
- Develop enhanced knowledge representation models and data exchange standards for complex systems which, at present, are 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 the literature, beyond and above simple pair-wise relationships between entities;
- Develop innovative and powerful data exploitation tools, for example multi-scale modelling and simulation, considering and integrating from the molecular to the systems biology level, and from the organ to the living organism level;
- 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 an expert tool (services/data negotiator) to guide users through the complexities of the data, data models, simulation and modelling tools and so on.

Education and Training

The SRA provides recommendations on new paradigms for conducting contemporary biomedical R&D which will have an impact on medical practice. To address the Education and Training bottlenecks in discovering and developing new medicines, the following five recommendations have been agreed:

- Establish a European Medicines Research Academy (EMRA), including a central co-ordinating unit and an advisory Education and Training (E&T) council;
- Establish programmes for integrated medicines development and for ethics committees and patient organisations;
- Establish programmes for safety sciences, scientists within pharmaceutical R&D and pharmaceutical medicine professionals;
- Establish regulatory affairs-based programmes;
- Establish programmes for biostatisticians, bioinformaticians and biomedical informaticians.

In summary, a total of 38 multi-disciplinary recommendations are presented within the Four-Pillars of the SRA. The complexity of contemporary biomedical R&D requires a combined multi-disciplinary approach to ensure patients benefit from advances in biotechnology. These advances, which include the decoding of the human genome, require a combination of both traditional and contemporary biomedical scientific excellence to create synergies between private and public sector capabilities. In essence, pan-European public and private sector collaboration and co-ordination is essential to ensure that patients benefit from advances in biotechnology, as the scientific challenges facing Europe are too complex for organisations to address in isolation.

This opinion is supported by *Nature Reviews Drug Discovery*:

*Greater collaboration between regulatory authorities, industry and academia is increasingly acknowledged as the answer to some of the thorniest problems in drug development, such as validation of biomarkers of efficacy and toxicity*⁶.

1.2 Stakeholder Involvement

1.2.1 Developing the Strategic Research Agenda

The Strategic Research Agenda (SRA) is the product of an extensive long-term consultation with stakeholders in the biomedical R&D process that commenced on the 5th and 6th October 2004, when the European Commission organised an initial consultation of stakeholders in Brussels. This consultation resulted in the following two main conclusions:

- The need for more information exchange between the different entities involved in biomedical research was identified as critical.
- The forum agreed with the list of issues to be addressed as proposed by the Research Directors from the pharmaceutical and biotechnology companies.

A report of this meeting can be found at:

ftp://ftp.cordis.lu/pub/lifescihealth/docs/tp_inmed_conclusions_meeting_5-6_oct_final1.pdf

Following this initial consultation, the European Commission and EFPIA organised a series of thematic workshops to develop the SRA. Since January 2005, a diverse and balanced group of 350 stakeholders, including R&D experts, regulators and patient group representatives from across Europe, have been consulted in the development of the SRA, and they have contributed to its recommendations. Figure 5 below illustrates that 48% of the contributors to the SRA originate from academia and SMEs. The characteristics of all contributors are presented in Figure 5, and they are listed individually in appendix 8.1 (page 123). This consultation culminated in an intensive discussion with all stakeholder representatives in Barcelona on the 21st and 22nd April 2005. A report of this meeting can be found at: http://www.eufeps.org/document/pdfs/nsmf_III_final_report.pdf

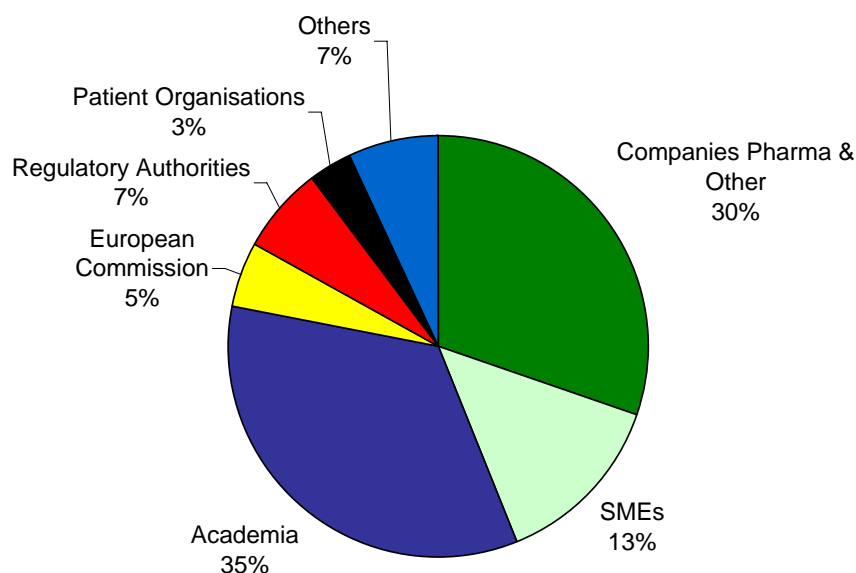


Figure 5 : Stakeholder Analysis of Contributors to the SRA

⁶ Editorial (2006). *Nature Reviews Drug Discovery*; 5: 267.

1.2.2 Updating the Strategic Research Agenda

In addition to their contribution to the preparation of the first versions of the SRA, all stakeholders have the opportunity to propose updates to the SRA based on new scientific or technological developments relevant to the objectives and scope of the SRA. The IMI Executive Office will define and communicate the detailed process for updating the SRA when the IMI legal entity is approved and operational.

1.2.3 Collaborating with other European Technology Platforms

European Imaging industry and public institutions have started to collaborate on the creation of a Strategic Research Agenda (SRA) for the NanoMedicine European Technology Platform. The vision paper was published in September 2005⁷. NanoMedical developments range from nanodiagnostics (lab-on-a-chip) and molecular imaging, through targeted drug delivery, controlled release and monitoring using carrier particles, to regenerative medicine. It is easy to envision a number of potentially successful collaborations within projects that originate from both IMI and NanoMedicine. In this context, both SRA teams have engaged in a dialogue, have agreed to exchange SRAs, to comment on them, and to inform and involve each other in calls for proposals and project work that involves disciplines such as:

- Molecular imaging modalities for both pharmacology and the clinic and disease specific imaging;
- Networks and communities of experts, standards setting for imaging in biopharmaceutical R&D;
- Development and validation of imaging biomarkers, targeted imaging contrast agents and tracers;
- A new and improved science-based regulatory approval process and healthcare delivery processes.

1.3 Contributions to Standards

IMI will not contribute to international standards *per se*, but by implementing the 38 multi-disciplinary recommendations described above it will enable new approaches to drug discovery and development to be evaluated and implemented more systematically and objectively.

The potential of IMI to create a new drug discovery and development paradigm is based on a more systematic use of biomarkers and on applying innovative technologies such as omics technologies and other types of data, in combination with appropriate knowledge management capabilities. One of the main objectives of IMI is to ensure all stakeholders are more closely involved in the enhancement of the biomedical R&D process. This includes discussion with representatives from regulatory authorities at an early stage of the biomedical R&D process and, therefore, IMI can be expected to facilitate a smooth transition of new basic scientific knowledge into regulatory standards.

In addition, the results of the implementation of the SRA recommendations will provide valuable input to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and thus have broad long-term international impact and benefit to society.

IMI may also contribute to further co-operation between the EMEA and the FDA, particularly as in March 2004 the FDA released a pivotal white paper entitled: *Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products*⁸. This document was intended to highlight the need for targeted collaborative efforts to modernise the tools, techniques and methods used to evaluate the safety and efficacy of drug products⁹. In March 2006, the FDA published the 'Opportunities List', which identified six areas of priorities. These are consistent with the Four Pillars of the IMI SRA. The topics are:

- Topic 1: BETTER EVALUATION TOOLS – Developing New Biomarkers and Disease Models to Improve Clinical Trials and Medical Therapy;
- Topic 2: STREAMLINING CLINICAL TRIALS – Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints;
- Topic 3: HARNESSING BIOINFORMATICS – Data Pooling and Simulation Models;
- Topic 4: MOVING MANUFACTURING INTO THE 21ST CENTURY;
- Topic 5: DEVELOPING PRODUCTS TO ADDRESS URGENT PUBLIC HEALTH NEEDS;

⁷ European Technology Platform on NanoMedicine: Nanotechnology for Health. Vision Paper and Basis for a Strategic Research agenda for NanoMedicine. September 2005. ISBN 92-894-9599-5.

⁸ FDA (2004) Innovation Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products.

⁹ Editorial (2006). *Nature Reviews Drug Discovery*, 5: 267.

- Topic 6: SPECIFIC AT-RISK POPULATIONS – Unlocking Innovation in Paediatric Products

If the use of biomarkers is generalised for pre-clinical and clinical investigations, IMI will contribute to standards by generating intensive discussions within the proposed networks on agreeing new approaches and European standards to validate biomarkers, as well as 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 IMI is to change the way the different stakeholders work together, establishing a new type of collaboration between industry, academia, clinicians, patients and, indeed, regulators. This would represent a true paradigm shift in culture as illustrated by the following quote:

Perhaps the biggest sociological divide in pharmaceutical sciences – the gap between academic and industry scientists. Put bluntly the sooner academic and industry scientists destroy the stereotypes they hold for each other, the more likely that drug discovery and development will truly evolve to succeed in the 21st century.

1.4 Impact of IMI on the Use of Animals in Research and Development

The problem with drug discovery is simple to state – too many projects flounder because the medicines being developed either do not work well or are unsafe (Figure 1). A considerable proportion of the enormous expense of drug discovery is a result of the cost of attrition along the path from basic research to approval and marketing. To this financial cost can be added the use of animals which has borne little benefit if the compound does not become a medicine. Increasing the success rate of drug discovery through IMI would, therefore, have an impact on animal use. The development of new technologies in drug discovery may increase the use of animals in research as described below. In the medium term, application of new technologies should refine and reduce the use of animals and help replace their use. This is an example of how EFPIA fully supports the concept of the ‘3Rs’. In addition, EFPIA along with its members is an active participant in the European Partnership for Alternative Approaches to Animal Testing¹⁰. EFPIA’s position paper on animal research and welfare can be read in appendix 8.2 (page 133). 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).

The IMI makes several recommendations which have implications for the 3Rs. First, the increased use of *in vitro* and *in silico* techniques to predict and profile the behaviour of drugs in animals could replace some current *in vivo* tests. This may also refine the use of animals in the identification of compounds with undesirable properties as they are more likely to be screened-out prior to animal testing. For some compounds, this high-throughput screening may reduce the animal data required to select suitable candidates for clinical trials. Second, the development of biomarkers which predict clinical efficacy or safety issues could promote reduction of animals in the long-term through more predictive animal tests with measures that provide more meaningful data, as well as decreasing the number of compounds tested as a result of earlier detection of unsuitable candidates. Furthermore, biomarkers for early indications of serious toxicity (i.e. using premonitory markers to identify a surrogate endpoint) could benefit **R**efinement by minimising animal distress. However, it should be recognised that the evaluation and validation of biomarkers could lead, in the short term at least, to an increase in animal research. The rigorous application of all 3Rs is, therefore, essential. Third, a major issue in toxicology is the relevance of some common rodent findings to toxicology in man. For example, while rodent models are the only reliable way for experimental investigation of non-genotoxic carcinogenicity risk of compounds to humans, interpretation of findings is often difficult. Understanding the mechanistic basis of genotoxic carcinogenicity could lead to the replacement of existing long-term tests with *in vitro* assays or short-term testing in animals. There are several other similar issues, collectively termed ‘intractable toxicities’, which will be investigated by the IMI, all of which could have profound 3Rs implications. Fourth, the development of more predictive animal models of disease will result in fewer molecules and concepts failing in the clinic on the grounds of efficacy after they have been extensively tested in non-GLP and GLP animal studies in order to get them to this stage. Fifth, successful pre-competitive data sharing through the IMI could—and should—lead to faster drug development and reduced attrition, with consequent implications for the reduction of the number of animals used.

¹⁰ http://ec.europa.eu/enterprise/epaa/index_en.htm

The Strategic Research Agenda aims to accelerate modern advanced experimentation, to constructively challenge practices in toxicology, to emphasise the use of surrogate end-points in research and clinical development, and place more emphasis on man as the experimental model of choice. Its successful implementation will, inevitably, have positive consequences for the 3Rs.

1.5 Key Benefits of IMI

It is important to appreciate that IMI will not—and is not expected to—deliver new medicines *per se*. However, it is expected to deliver powerful new multi-disciplinary tools to improve the innovation process and thus establish a new drug development paradigm.

Establishing a new drug development paradigm will support the faster discovery and development of better medicines, providing faster access of patients to new and innovative medicines.

The research currently being performed in the FP6 InnoMed Integrated Project which encompasses predictive toxicology (PredTox), and the discovery and validation of new biomarkers for diagnostics, disease progression and therapeutic efficacy in Alzheimer's Disease (AddNeuroMed) demonstrates the unique contribution that European Public–Private Collaborations can make in improving the biomedical R&D process.

The main benefits of IMI for patients, scientists and Europe are:

- Faster discovery and development of better medicines for patients;
- More attractive professional environment for scientists, addressing the 'brain drain';
- Better European expertise and know-how in new technologies to attract biomedical R&D investment in Europe;
- Stronger competitive advantage for small and medium-sized enterprises, spin-offs and start-ups to enhance Europe's economy.

1.6 The Biopharmaceutical Sector's Contribution to the Lisbon Agenda

The pharmaceutical and biotechnology sector impacts upon the daily lives of citizens, but also accounts for a large proportion of Europe's GDP¹¹. Europe's (EU-25) biopharmaceutical industry produced a trade surplus of €24.1 bn in 2004, a significant amount, which has been growing at 11.4% per year since 2000 (4Y CAGR 2000–2004). On this basis, it can be estimated that the trade surplus of Europe's biopharmaceutical industry reached approximately €27 bn in 2005, as illustrated in Figure 6 below.

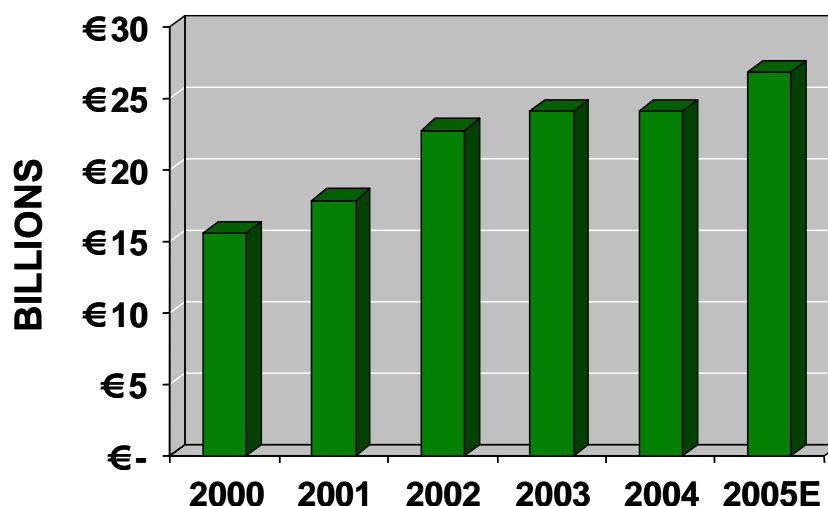


Figure 6 : Trade Surplus of Europe's Biopharmaceutical Industry 2000–2005¹²

¹¹ Aho E, Cornu J, Georghiou L, Subirá (2006). Creating an Innovative Europe – Report of the Independent Expert Group on R&D and Innovation Appointed Following the Hampton Court Summit, European Commission, Luxembourg.

¹² European Commission, Eurostat, SITC 54, Luxembourg.

The biopharmaceutical sector has Europe's largest high-tech sector trade surplus, and provided employment for more than 500,000 people in 2004 (Figure 7). A high proportion of these perform highly skilled knowledge-based R&D roles. Employment in biopharmaceutical R&D has been growing at 4.2% per year since 2000 (4Y CAGR 2000–2004). The trade surplus and employment statistics (both total and R&D only) can be considered to be conservative as they do not include data from Switzerland.

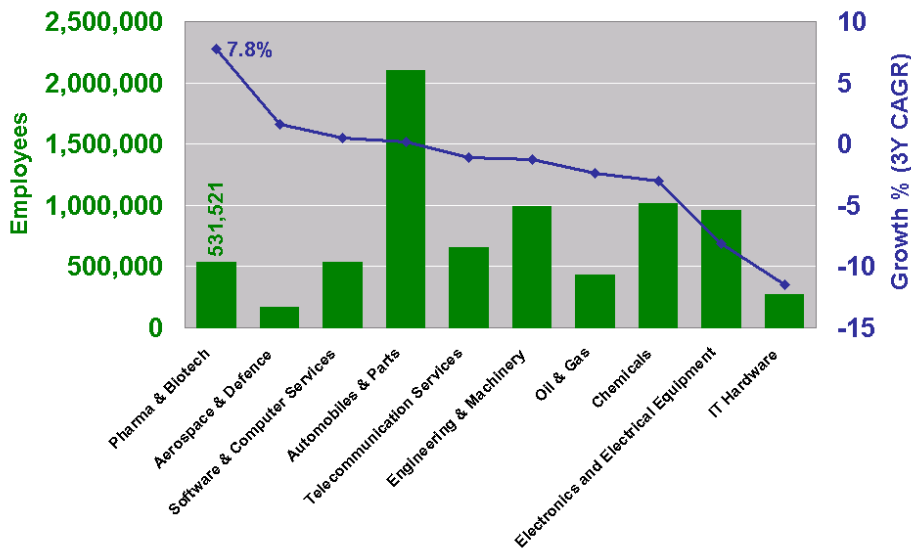


Figure 7 : R&D Employees of Europe's Biopharmaceutical Industry 2004¹³

According to the 2005 EU Industrial R&D Investment Scoreboard the pharmaceuticals and biotechnology sector invested a total of €17.7 bn in R&D in 2004, making it Europe's second-highest R&D investing sector after Automobiles and Parts. However it is the leading sector in terms of R&D investment growth which reached 11.9% between 2001 and 2004 (3Y CAGR). Over the same period, employment in the pharmaceuticals and biotechnology sector grew by 7.8% (3Y CAGR 2001–2004). These statistics demonstrate that the biopharmaceutical industry is Europe's most dynamic R&D sector, and a key contributor to the Lisbon Agenda.

Europe is seen as a less attractive R&D investment location in terms of market conditions and incentives for the creation of new biotech companies¹⁴. In 2005, the US biotechnology industry invested a total of €12.8 bn in R&D, which represented 79% of global biotechnology R&D investment, and a positive growth rate of 2.3% (3Y CAGR 2003–2005). In comparison, as illustrated in Figure 8 below, the European biotechnology industry invested a total of €2.7 bn in R&D in 2005. This represented 16% of global biotechnology R&D investment, and a negative growth rate of -10.9% (3Y CAGR 2003–2005). On average, European-based public biotechnology companies invested €22 mn per company in R&D in 2005, whereas their US counterparts invested €39 mn per company in R&D.

¹³ European Commission (2006). The 2005 EU Industrial R&D Investment Scoreboard, Luxembourg

¹⁴ EFPIA (2006). The Pharmaceutical Industry in Figures, 2006 Edition, Brussels.

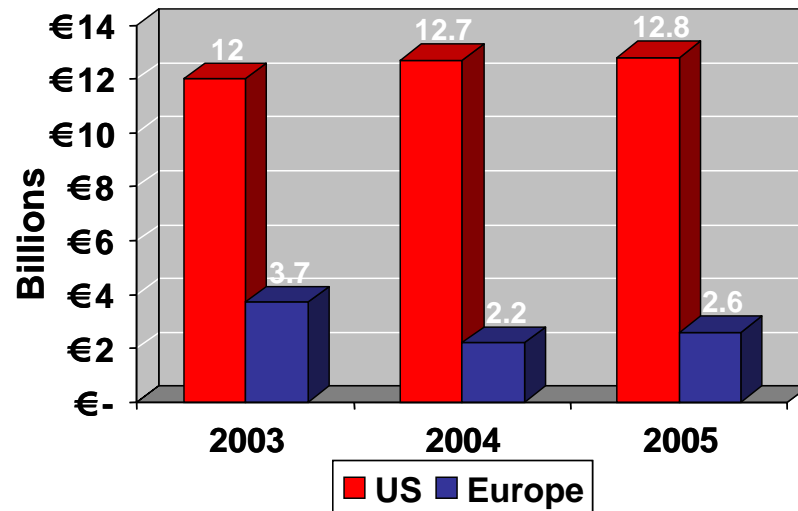


Figure 8 : Global Biotechnology R&D Investment by Company Origin 2003–2005¹⁵

Throughout the world, the biosciences rank prominently in the economic development agendas of governments because progress in microbiology and genomics hold the promise to make biotechnology the dominant economic force of the first half of the 21st century^{16 17}. At the Lisbon Summit in 2000, the European Council set a clear strategic objective: to transform Europe into the world's most competitive and dynamic knowledge-based economy by 2010 – an economy characterised by a R&D Intensity of at least 3%, and with two-thirds of its total R&D expenditure originating from the business enterprise sector¹⁸. The European Council regards R&D as the driving force behind economic growth, job creation and innovation of new products in general, as well as improvements in healthcare. However, while R&D Intensity for Europe has shown a positive growth rate in the six years up to 2003, it currently lags behind that of the US and Japan, and is being seriously challenged by China, as illustrated in Figure 9 below.

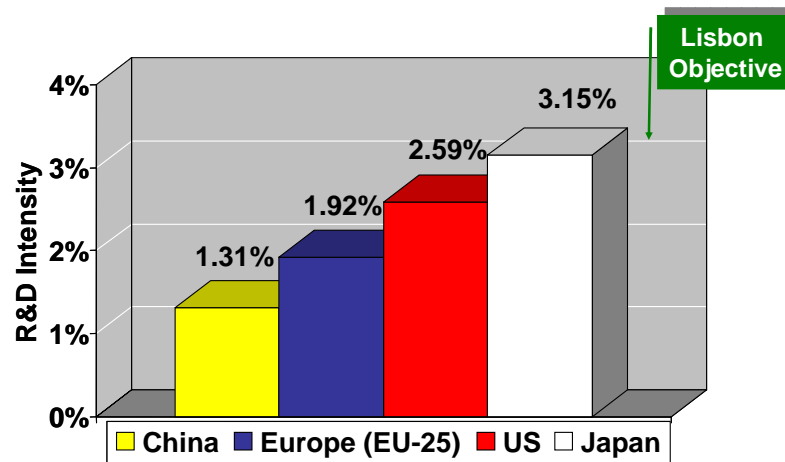


Figure 9 : Comparison of R&D Intensity

Furthermore, Figure 10 confirms the argument above by demonstrating that the growth rate of China's R&D Intensity (4Y CAGR 1999–2003) out-performed all other leading economies, and was a staggering 17 times higher than that of the EU-25.

¹⁵ Ernst & Young (2006). Global Biotechnology Report.

¹⁶ Rinaldi A (2006). More than the sum of their parts?, *EMBO Reports*; 7, 2: 133–136.

¹⁷ DeVol R, Wong P, Ki J, Bedroussian A, Koepf R (2004). America's Biotech and Life Science Clusters: San Diego's Position and Economic Contributions. Santa Monica, CA, USA: Milken Institute.

¹⁸ European Commission (2006). Europe in Figures, Eurostat Yearbook 2005, Luxembourg.

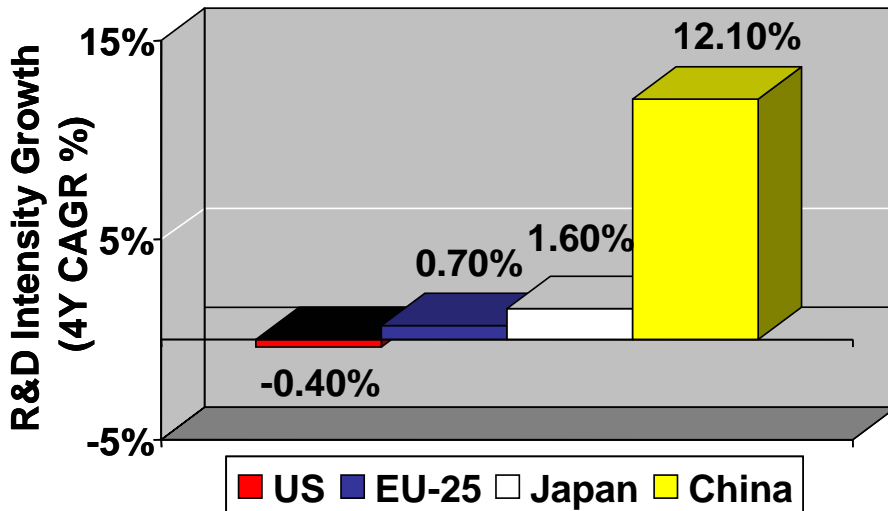


Figure 10 : Comparison of R&D Intensity Growth

Recent data on the R&D Intensity of the EU-25 suggests that the Lisbon objective is in jeopardy without a significant injection of new R&D investment from both the private and public sector, as illustrated by the following quote from the recent Aho report:¹⁹

It is well known that the 3% target cannot be approached without a very substantial increase in business investment in R&D and innovation.

Government support for R&D in the EU-25, as measured by GBAORD, is lower than it is in the US, and only marginally higher than Japan, as illustrated in Figure 11 below.

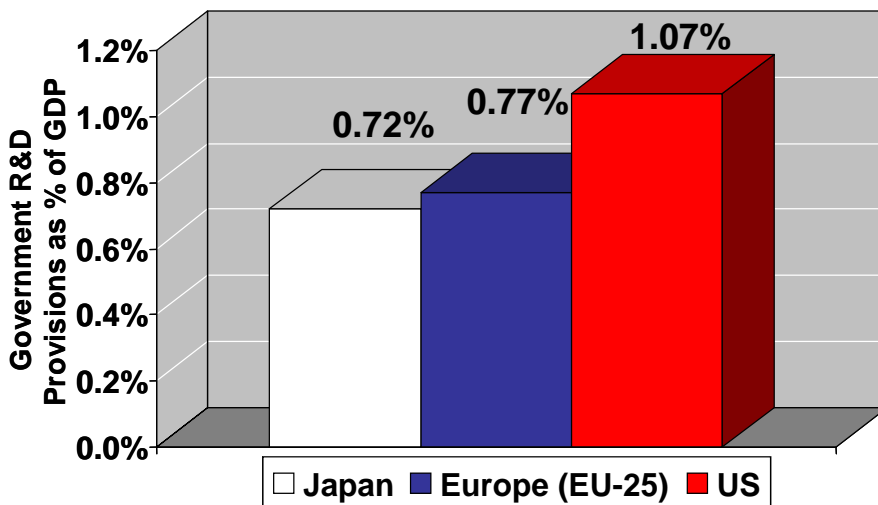


Figure 11 : Comparison of Government Support for R&D (GBAORD)²⁰

The overall pattern of R&D under-investment in the EU-25 described above is also true for biomedical R&D. This point is demonstrated in Figure 12 below, which highlights the fact that, in the US, a far greater proportion of GDP is directed to public sector sponsored biomedical research than in Europe (EU-15).

¹⁹ Aho E, Cornu J, Georghiou L, Subirá (2006). Creating an Innovative Europe – Report of the Independent Expert Group on R&D and Innovation Appointed Following the Hampton Court Summit, European Commission, Luxembourg.

²⁰ European Commission (2006). Europe in Figures, Eurostat Yearbook 2005, Luxembourg.

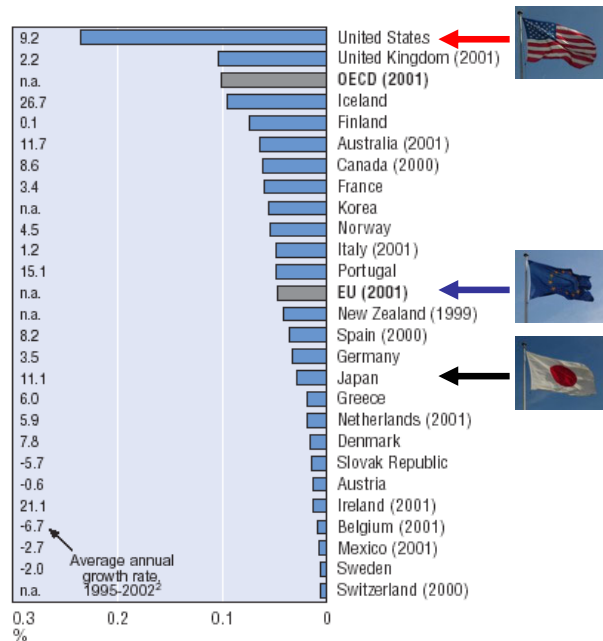


Figure 12 : Health R&D in Government Budgets as a Percentage of GDP, 2002²¹

Figure 13 below provides examples of national spending on biomedical research in selected Member States as well as the US. The total spending for the selected European organisations was € 3.6 bn in 2005. Although this does not represent the entire public biomedical research spending in Europe, it illustrates the level of under-funding in the EU-25 in comparison to the US. In addition, the fragmented nature of the biomedical research environment in Europe makes it difficult to optimise resources by creating pan-European synergies for the benefit of patients.

Research Funding Agency (Country)	Spending 2005 (€mn)
National Institutes of Health (USA)	23,000
Ministry for Science & Technology – Life Sciences (Japan)	3,015
Medical Research Council & National Health Service (UK)	1,750
Max Planck & Deutsche Forschungs Gemeinschaft (Germany)	778
FP6 ‘Life sciences, genomics & biotechnology for health’ (EU-25)	564
Institut National pour la Sante et la Recherche Medicale (France)	475
Karolinska (Sweden)	413
Consiglio Nazionale delle Ricerche (Italy)	174

Figure 13 : Examples of National Biomedical Research Funding in 2005

1.7 R&D Performance

Between 1998 and 2003, the US Government increased its funding of the National Institutes of Health (NIH) by 200% to \$27 bn. This fact can be interpreted as a commitment by the US government to winning the ‘R&D Race’. Should the US win this race, it would not only have serious repercussions for Europe’s economy but, more importantly, would exacerbate the serious issue facing Europe of delayed patient access to new innovative medicines. Based on NME approvals (which can be used as an indicator of innovation performance), US based biopharmaceutical companies are currently winning the ‘R&D Race’. This position is supported by the fact that US-based biopharmaceutical companies gained the highest number

²¹ OECD (2003). R&D Database, Paris.

of NME approvals between 1986 and 2005 – despite running second to Europe throughout the preceding decade (see Figure 14 below). Between 1960 and 1965, European-based companies invented 65% of new chemical entities (NCEs) placed on the world market. Forty years later, their share had fallen to 34%. The latest data available, for the period 2001–2005, show the dominance of the United States, which has now become the leading inventor of new molecules in the world²².

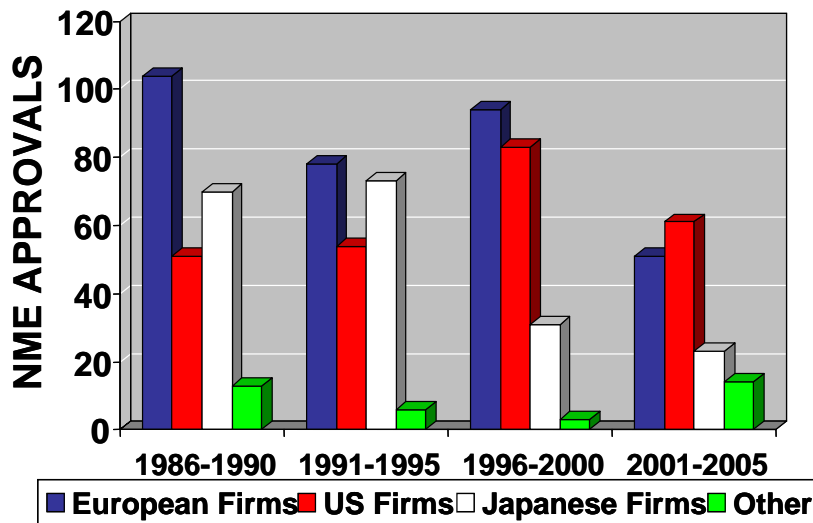


Figure 14 : Global NME Approvals 1986–2005

When comparing the innovative performance of European-based biopharmaceutical companies to those based in the US on the basis of FDA approved new cancer medicines (Figure 15), the innovation performance of Europe is even more alarming because oncology is an innovative therapeutic area that has produced breakthroughs in targeted therapy, such as Glivec[®] and Herceptin[®].

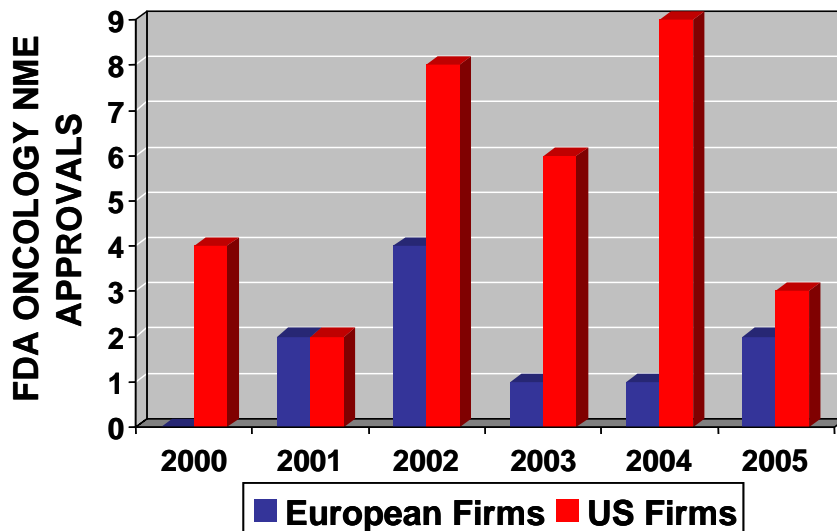


Figure 15 : FDA Oncology NME Approvals 2000–2005²³

Even more disturbing for patients with unmet medical needs is the fact that US patients are gaining access to better medicines faster than Europeans as the US remains the region of choice for first launches, accounting for almost 50% of all global NMEs first launched in 2004. This is illustrated in Figure 16 below.

²² EFPIA (2006). The Pharmaceutical Industry in Figures, 2006 Edition, Brussels.

²³ FDA <http://www.fda.gov/cder/cancer/approved.htm>

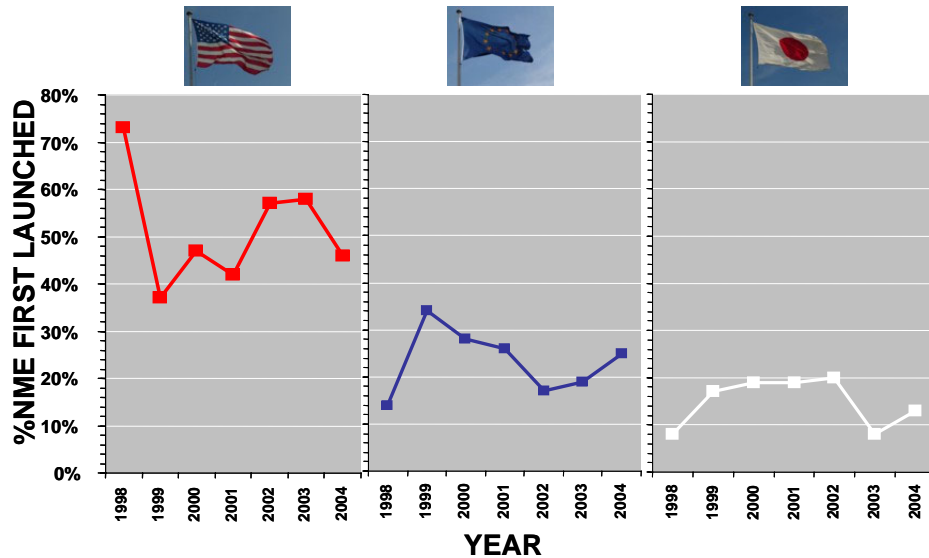


Figure 16 : Regions of First Launches of NMEs 1998–2004²⁴

Overall, the range of macro-economic indicators presented above support the conclusion that the biopharmaceutical industry is an essential sector for meeting the Lisbon objective of 3% R&D Intensity, and for Europe to continue to compete effectively with other economies in the future. However, Europe’s biomedical R&D base is actually diminishing in comparison with the US. Between 1990–2005 R&D investment in biomedical sciences in the US increased by more than 460% while, over the same period, R&D investment in biomedical sciences within Europe increased by just 280%²⁵. The pattern of relative underinvestment is illustrated with a sample of data from 2000–2005, described in Figure 17 below:

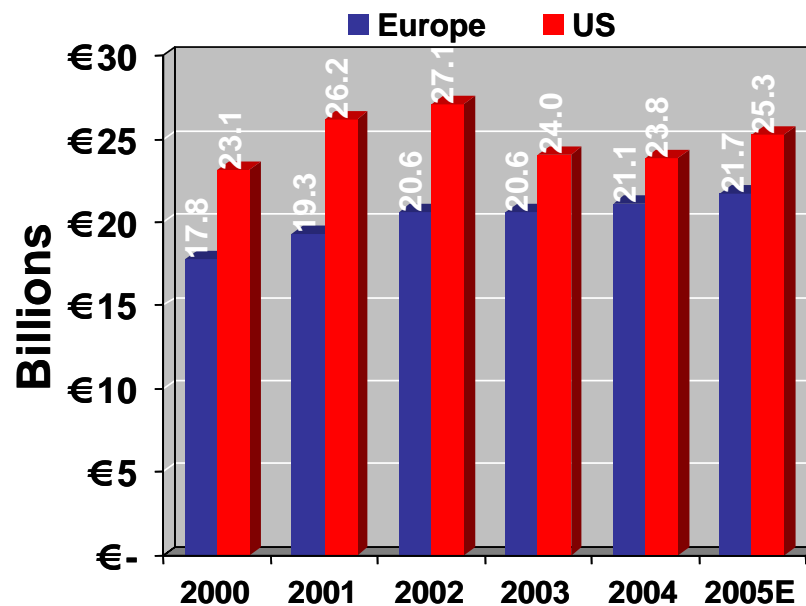


Figure 17 : Comparison of European and US Pharmaceutical R&D Expenditure 2000–2005

In 1990, the major European research-based pharmaceutical companies invested 73% of their global R&D budgets within Europe. By 1999, this amount had declined by 19% to 59%. The US was the main beneficiary of this trend, evolving to become the preferred destination for the transfer of biomedical R&D assets in 2005. In addition, the biopharmaceutical companies have created R&D centres in Asia, predominantly in Japan, China and Singapore.

²⁴ Centre for Medicines Research International Ltd. CMR International 2005/2006 Pharmaceutical R&D Factbook (2005)

²⁵ EFPIA (2006). The Pharmaceutical Industry in Figures, 2006 Edition, Brussels.

Europe's research-based biopharmaceutical industry invested €21.1 bn on R&D in Europe in 2004 , which can be divided into the four key areas listed below:

AREA	INVESTMENT (€bn)
Discovery & Pre-clinical Development	6.8
Phase I	1.5
Phase II	2.3
Phase III, Registration and Pharmacovigilance	10.5
Total	21.1

Should this trend of relative under-funding of biomedical R&D investment continue within Europe's pharmaceuticals and biotechnology sector, then it is clear that the European Union's Lisbon objective must be re-assessed, because R&D assets are widely recognised as the pipeline of technological innovation, and levels of R&D investment is a reliable indicator of innovation capacity²⁶ .

Data contained in the 2005 European Innovation Scoreboard highlights the innovation gap between Europe and other economies, and reported that it would take 50 years for Europe to reach the US level of innovation performance²⁷ . It can be concluded that, on the basis of this information, that the innovation capability of Europe and, thus, its competitiveness, is being weakened for the future by the current level of R&D investment. This position is supported by the following quote from the Aho report:

The current trends lead us to a position outside the world's top economic powers by 2030²⁸ .

The Innovative Medicines Initiative seeks to address the economic issues described above for the benefit of patients and Europe. This is supported by the following quotes:

Europe and its citizens should realise that their way of life is under threat but also that the path to prosperity through research and innovation is open if large scale action is taken now by their leaders before it is too late.

Examples of areas of science and technology where Europe needs to invest today so as not to face a gap analogous to that what we see in ICT include biotechnologies, cognitive and neuro-sciences.

²⁶ DeVol R, Wong P, Ki J, Bedroussian A, Koepf R (2004). America's Biotech and Life Science Clusters: San Diego's Position and Economic Contributions. Santa Monica, CA, USA: Milken Institute.

²⁷ European Commission (2006). European Innovation Scoreboard 2005. European Trend Chart on Innovation. Luxembourg.

²⁸ Aho E, Cornu J, Georghiou L, Subirá (2006). Creating an Innovative Europe – Report of the Independent Expert Group on R&D and Innovation Appointed Following the Hampton Court Summit, European Commission, Luxembourg.

1.8 Signatures of the EFPIA Research Directors' Group Members

The Research Directors' Group of EFPIA consists of senior management responsible for R&D activities in the pharmaceutical industry in Europe. The group has the strategic leadership of IMI, and works actively to ensure its successful implementation.



P.H. Andersen / H. Lundbeck A/S



A. Busch / Bayer HealthCare




H. Buschmann / Esteve



E. Canet / Servier



D. De Chaffoy de Courcelles /
Johnson & Johnson



A. Chiesi / Chiesi Farmaceutici S.p.A



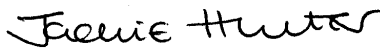
F. Gvillo / Schering AG



P. Herling / Novartis AG



R. Hill / Merck & Co



J. Hunter / GlaxoSmithKline



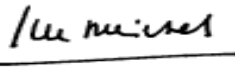
C. Incerti / Genzyme



J. Knowles / F. Hoffmann-La Roche Ltd



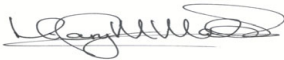
P. Kurtzhals / Novo Nordisk A/S



J. Kusmierek / Pierre Fabre
Médicament



J. Lundberg / AstraZeneca



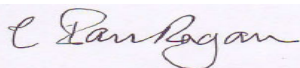
H. Malone / Wyeth



M. Pairet / Boehringer Ingelheim
GmbH



A. Puech / Sanofi-Aventis



C. Ragan / Eli Lilly & Co



R. Rappuoli / Novartis Vaccines



D. Roblin / Pfizer



L. Turski / Solvay S.A.



F. Weber / Merck KgaA



N. Weir / UCB



T. Wells / Serono S.A.

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. A project has been proposed to enhance the prediction of toxicity by integrating the new omic technologies with conventional toxicity endpoints, and this has been submitted under the 6th Framework Programme (FP6). This is anticipated to bring in some increases in predictivity, but major additional gains may also result.

It is proposed that a small European Centre of Drug Safety Research (ECDSR) should be formed. This would co-ordinate research efforts in the area, enhance the training and education of drug safety scientists, and realise the benefits of knowledge management in this area. Specific research projects are described below that the proposed centre would co-ordinate. These are: creating a framework for biomarker development, including the FP6 project; determination of the relevance of non-genotoxic carcinogens; development of better and more widely applicable *in silico* models of toxicity; and developing a better understanding of so-called 'intractable toxicities'.

ECDSR ('Centre') was initially intended to focus on non-clinical issues, but subsequent discussion established that there was an urgent need to integrate pharmacovigilance and risk management into the activities of the Centre. This is a result of new concepts which support proactive pharmacovigilance throughout the life-cycle of medicinal products. These processes are not just a one-off exercise to launch a medicine onto the market, but extend all the way from initial non-clinical investigation through to clinical investigation, and then to its use in real life. The aim of the process would be to improve the availability and safe use of medicines by effective pharmacovigilance and risk management.

The main recommendations concerning Safety Evaluation are:

- Create a European Centre of Drug Safety Research 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 animals for the risk in humans;
- Optimise data resources and strengthen the evidence base in pharmacovigilance;
- Develop and strengthen methodologies and networks of pharmacovigilance;
- Develop novel methods for risk prediction and risk–benefit assessment;
- Training and education of health care professionals and patients.

An estimate of the funding that will be needed to set up and run the Centre and to support the chosen projects is included.

2.2 Introduction

If the predictivity of early safety evaluation can be improved to cut the rate of attrition in drug development, greater efficiencies will result. There should also be a realistic appreciation of what animal based tests can and cannot provide to regulators in terms of understanding drug safety in humans.

The process of improving the predictivity of safety evaluation can best be achieved by an international collaborative approach. The Innovative Medicines Initiative 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 medium-sized enterprises with expertise in the necessary disciplines, for example software-developers, database providers, chip producers and other technology manufacturers;
- Small and medium-sized enterprises involved in advanced pharma research with innovative targets;
- European university laboratories with focused expertise;
- European regulatory agencies;
- The Health Environmental Sciences Institute, which has started an initiative on non-clinical-clinical safety correlation;
- A working group that includes members of the Innovative Medicines Initiative (Education & Training; Knowledge Management) and experts from EUFEPS;
- The Toxicogenomics working group of the InnoMed consortium member EFPIA companies;
- Representatives from patient groups.

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 toxicities²⁹.

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

It will also lead to a reduction in adverse drug reactions; more rational use of experimental animals and, possibly, a reduction in the number required; more adequate regulatory requirements; and faster drug development. There will be animal welfare benefits if non-animal tests can replace or improve predictivity. This will be aligned with EFPIA's policy concerning the use of animals in R&D (appendix 8.2).

There are basically two different approaches to predictive toxicology:

- The 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.

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, which is the detection of 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 with the technologies above, this is carried out in the context of changes in response to exposure to a toxic compound.

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

There are several related projects ongoing in FP6, such as Predictomics, REPROTEC or A-Cute-Tox.

The main purpose of the PredTox Project being funded by FP6 is to evaluate the usefulness of these new technologies in pre-clinical safety testing, and to provide a functional database containing integrated information from the omics technologies with that from traditional toxicity endpoints for agents that cause liver or kidney toxicity. Once established, the challenge will be to share the application of these technologies in pre-clinical safety testing, and training and educating scientists from industry and in the regulatory authorities in their use and value.

²⁹ Nature Reviews Drug Discovery 3, 711-715, 2004

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

The ultimate goals must be to:

- Assess the value of combining results from omics technologies with the results from more conventional toxicology methods to enable more informed decision-making in pre-clinical 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, ultimately, agree on the approach for their use.

2.2.2 Pharmacovigilance and Risk Management

The origin of pharmacovigilance goes back to the thalidomide tragedy of the early 1960s. Birth defects caused by thalidomide then led directly or indirectly to medicines regulatory bodies being set up in some countries, and to the development of spontaneous reporting systems for adverse events. Over the subsequent four decades, 121 medicines were withdrawn from the market for safety reasons^{30,31}. As with the impact of adverse drug reactions, annual mortality varies from country to country (10,000 deaths in the UK,³² 100,000 in the USA³³). There is, therefore, as much need now as ever to improve the effectiveness of pharmacovigilance and, ultimately, the public health of EU citizens.

The definition of 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 administration³⁴.

Much of the current pharmacovigilance process is reactive, and primarily relies on the spontaneous reporting of adverse events. It is limited by under-reporting, as well as by data quality, which is often insufficient to permit the best possible assessment. Post-marketing regulatory decisions often need to be taken on the basis of a rather limited evidence base. There is, therefore, a pressing need to develop a more robust and proactive system for the risk management of medicinal products throughout their life-cycles.

Risk management is defined as a set of pharmacovigilance activities and interventions designed to identify, characterise and prevent or minimise risks relating to medicinal products, including risk communication, and the assessment of the effectiveness of risk-minimisation interventions³⁵.

For pharmacovigilance to be carried out more effectively in the future, it should be recognised that a wealth of data is already available in the EU concerning the use of medicines, both in the clinical trial setting and in clinical practice in the home and the hospital. These include epidemiological sources, and other databases which hold data on exposure to medicines and outcomes, including adverse events. However, a central repository of such data does not currently exist. In addition, it is not known if different data sources communicate with each other, or whether they can be combined to improve the evidence base and increase statistical power.

Systems and networks for pharmacovigilance exist for the purpose of regulation, but not for research.

³⁰ Fung M. et al. Drug Information Journal 2001;35:293-317

³¹ Woodcock J. et al. JAMA 1999; 281:1728-1734

³² Pirmohamed et al. BMJ 2004; 329; 15-19

³³ Lazarou J. et al. JAMA 1998; 279:1,200-1,205

³⁴ WHO 2002. The importance of Pharmacovigilance Safety monitoring of medicinal products ISBN 9241590157

³⁵ EMEA/CHMP/96268/2005

In terms of the methodologies used for pharmacovigilance, these have remained largely unchanged over the past two decades. However, in terms of risk management, there are, as yet, insufficient methods for risk minimisation available for testing. Risk communication tools such as product information and ‘Dear Health Care Professional’ (HCP) letters have also been used for decades but their effectiveness has been put into question^{36, 37}.

As the overall aim of pharmacovigilance is the safe use of medicines by HCPs and patients, there is tremendous scope for targeted education and information.

2.3 The European Centre of Drug Safety Research

Based on workshops held with experts from all the above-mentioned stakeholders on the topic of safety, a priority proposal for future safety evaluation has been developed under the Innovative Medicines Initiative for implementation during the 7th Framework Programme (FP7).

The most urgent need identified by these groups to help achieve the goals above is to bundle together and organise all related activities as a nucleus for harmonisation.

A new structure, the European Centre of Drug Safety Research (ECDSR), will cover issues of non-clinical safety, pharmacovigilance and risk management, since the overall aim of these activities will be to improve safety of medicines in humans.

A detailed analysis of the specific needs and requirements was completed, and details on priority programmes are provided.

The Centre will be independent, and comprise a small group of core staff, alongside a wide network of associated and visiting 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, such as the development of databases, including knowledge management tools for data analysis in pharmacovigilance;
- Providing leadership and supporting professional education and training;
- Providing communication on drug safety issues to stakeholders and the media;
- Compiling and maintaining a safety data warehouse as an essential activity to support the other three areas;
- Optimisation of data resources and strengthening of the evidence base in pharmacovigilance;
- Development and strengthening of methodologies and networks of pharmacovigilance;
- Development of novel methods of risk prediction and benefit–risk assessment;
- Training and education of health care professionals and patients.

After performing 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 of Drug Safety Research. Figure 18 below contains a list of the main organisations and 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

³⁶ Smalley W. et al. JAMA 2000; 284: 3036-3039

³⁷ Graham D.J. et al. JAMA 2001; 286 No. 7: 831-833

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 and national regulatory authorities
European Commission	EU Health Authorities and Health Department
Identifiable patient groups	Deutsche Forschungs Gemeinschaft (DFG) D
Identifiable media organisations	
Academic centres of excellence in safety sciences	Surrey/Birmingham Uni – MSc program

Figure 18 : Examples of Organisations Involved in the Drug Safety Evaluation Process

The Centre would have limited permanent staff, but would have the benefit of a Europe-wide network of pre-clinical experts. There are well-established organisations, for example CMR International and HESI which are run by a small number of staff, that prove such a model would suit the proposed Centre (Figure 19). The overall governance of the Innovative Medicines Initiative is referred to in the ‘Governance and Funding’ chapter of the SRA document. The Centre should be located adjacent to an organisation with a good IT infrastructure. The Centre must be independent and should consist of:

- A scientific advisory board, with members nominated by the EC, pharmaceutical industry, academia, and regulatory authorities;
- The Centre will have two sections: non-clinical safety – predictive toxicology, and pharmacovigilance and risk management;
- Two directors, who will be senior safety scientists, as the ECDSR will cover the two completely different scientific disciplines of non-clinical safety and pharmacovigilance, and it is unlikely that it would be possible to find one director who would be capable of covering the two different scientific fields adequately;
- Project managers;
- Data mining/IT support personnel.

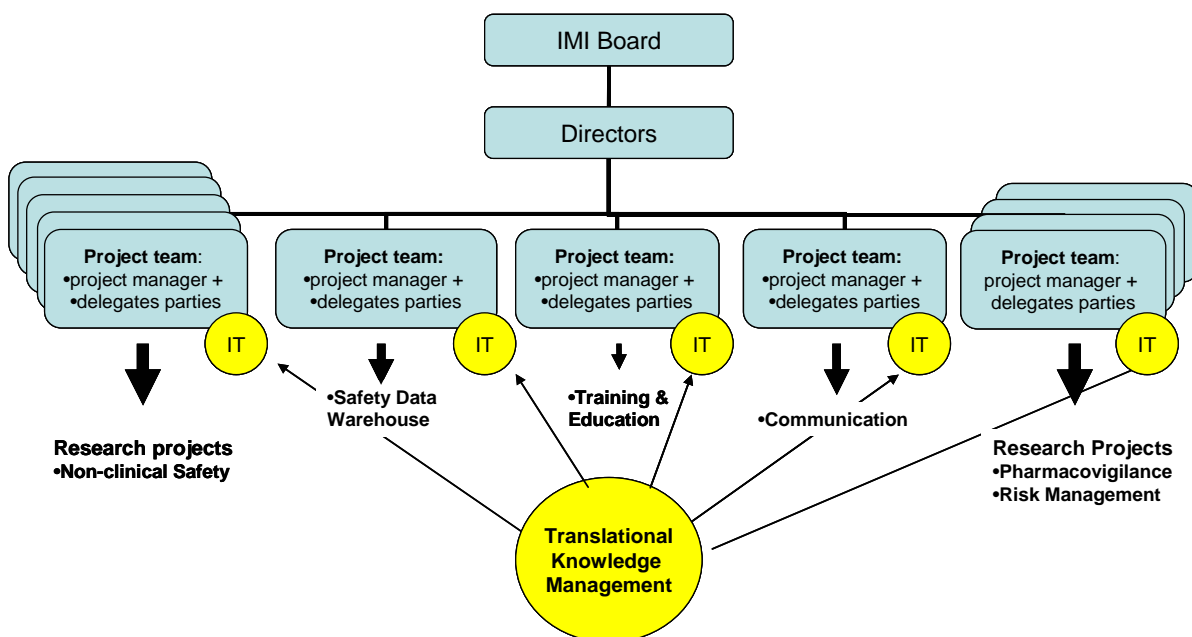


Figure 19 : Structure of the ECDSR and Interaction with Knowledge Management

Education & Training and Communication is of key importance to ensure a workforce will be available in drug safety evaluation for the future. Some of the key tasks of the ECDSR will be:

- Establish close co-operation / co-ordination with IMI-FP7–SRA experts of Pillar IV on ‘Education and Training’;
- Identify existing best practice, and co-ordinate and extend to other regions, for example to extend the UK CPD (Continuing Professional Development) to the rest of Europe, or Surrey MSc model (initial level) and higher level CPD;
- Map existing EU Member States’ training of the 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;
- Providing support for job rotations with other areas of safety science to allow relevant expertise to be spread more quickly;
- Address the issue of shortage of expertise in jobs such as toxicological pathologist, system biologist and animal technician.

EUFEPS has made available advanced ideas and elaboration on this topic, which will be incorporated.

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

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, and reduced cost and time of drug development. The key role the safety data warehouse can play has been explained above. It will, additionally, contribute to a positive public image of safety research. The role of ECDSR is:

- Close co-operation and co-ordination with IMI-FP7–SRA experts of the Pillar III on ‘Knowledge Management’;
- Collection, reference, validation, quality control (QC), maintenance, data searching and mining, and reporting, including the negative results that are not normally published by scientific journals, but which can be of great value in several areas, and also help with the reduction unnecessary animal testing;
- Definition of the boundaries of databases – the nature and level of data and organisation of data sharing between industry companies; specific issues of competition and proprietary information to be managed – with a possible incentive of the extension of exclusivity;
- Identification of areas to focus on, for example, excipients: all data will come from GLP toxicity studies with 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 chemical structural information if that is feasible;
- Clarification and management of access rights and restrictions of access to certain levels of data;
- Safety data warehouse management and maintenance.

The ECDSR will start-up with 12 envisaged **Research Projects**. Seven of these will be maintained on a permanent basis. These are communication, education, the safety data warehouse and four projects on pharmacovigilance and risk management. Research projects will be initiated each year, and supported on a temporary basis. In principle, each of these projects will be managed by a project team consisting of a project manager from the centre staff, and a number of delegates appointed by the various stakeholders.

Based on current needs and to give direction to the research activities part, the projected research projects are already defined in this proposal. These are explained below. 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 Centre becomes operational. Other additional and follow-up projects will be defined and initiated by the Centre itself.

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

There should be ‘quick wins’ through the improvement of active communication and measures regarding education.

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

- Research projects: the number of active research projects operational within two years. Project initiation should be faster in comparison to what happens at the moment. This is of particular importance as it would allow action to be taken quickly and adequately on important emerging general problems regarding drug safety;
- The number of students included in educational courses;
- The number of projects initiated, based on results of the database after the first four-year period;
- Successful development and implementation of safety models with improved predictivity.

2.4 Priority Areas for Research in Non-clinical Safety

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

- Identifying research needs in safety sciences and implementing and co-ordinating research programmes through a science board;
- Catalysing increased collaboration between industry, regulators, academia and other stakeholders;
- Provision of a point of reference and oversight for all FP7 projects, such as the extension of the FP6 PredTox activities;
- Giving advice on grant applications, and deciding on tenders for research proposals from FP7 and other proposals.

The safety data warehouse is considered to be a unique and essential tool in identifying and supporting research activities in this area. The specific role of this tool will be further described later in this 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 Centre to run such research projects, these proposals have been already implemented in this proposal (see below). The advantage will be that these projects can be initiated by the Centre during the time the safety data warehouse is being built up. The safety data warehouse is the tool that should support the definition of additional important research areas.

Following intense discussions, it has been determined that the two pillars of the Centre's research activities will 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. Further details are given below.

In addition, the two areas below are very important research needs that should be dealt with as soon as the Centre is operational, as individual research projects of priority:

- Development of *in silico* methods;
- The issue of intractable toxicities.

2.4.1 Framework for Biomarker Development

Within the ECDSR, a European framework for the development of safety biomarkers will be created, including platform / guidance for technology harmonisation, validation, data coherence and bioinformatics.

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

These activities should particularly help the exploitation of the extended FP6 liver and kidney study (the PredTox part of the 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 idealised (pre-clinical/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/pre-clinical 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 to them;
- 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 the number of individuals tested, whether animals or humans.

The overall strategy is to influence, support, work with and build on existing programs and EU projects, for example the PredTox part of InnoMed program; other EU FP6 IP programmes, such as Predictomics, Reptec or A-Cute-Tox; and the ILSI/HESI Biomarker subcommittee.

Each new candidate biomarker requires validation in the pre-clinical and clinical arenas, and the minimal biomarker pre-validation package prior to acceptance is shown in Figure 20 below. To achieve general acceptance, in-house validation is not sufficient, as has been 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 ECDSR Research Project.

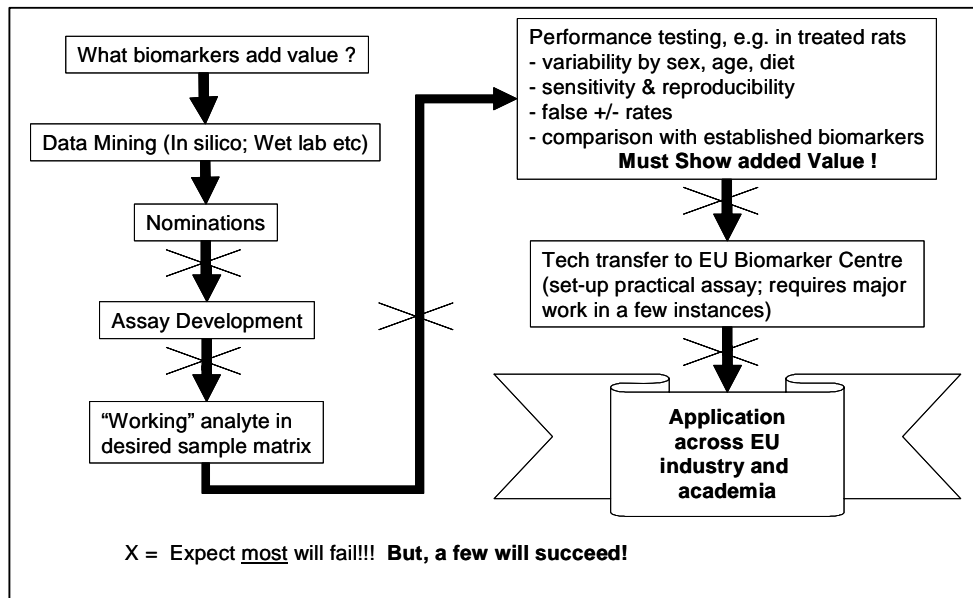


Figure 20 : Minimal Biomarker Pre-Validation Prior to Acceptance

Implementation within the ECDSR will be as for any other research project: the development of an individual biomarker (or a limited set of directly linked biomarkers) will be allocated to a project team as described in Figure 20 above. Thus, depending on the number of candidate biomarkers identified, a number of research projects will be initiated. A separate Biomarker Strategic Management Team comprising selected members and project managers from the individual Research Projects will be given the task of prioritising, accepting, rejecting and cancelling 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 pre-clinical species;
- Validation in a sufficient number of clinical studies;
- Mechanistic understanding;
- Data analysis.

This requires extensive work that exceeds the resources of individual institutes or companies. Neither is it the core business of pharmaceutical companies.

Metrics of success and duration of the project:

- The 'quick-wins' will be the 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 would be mid- and long-term measures of success;
- The duration of the project may be longer than 10 years, with cyclical reviews of performance by the parties involved.

2.4.2 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 occur 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 that currently has a high priority is receptor-mediated carcinogenesis, for example as demonstrated by the peroxisome proliferator-activated receptor (PPAR) carcinogenicity issue.

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

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 and omics approaches to the development of predictive markers for non-genotoxic carcinogenicity;
- Evaluation of alternative approaches, such as alternative carcinogenicity studies of shorter duration, sub-chronic studies in aged animals or the 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 better understand the relevance of rodent studies for the prediction of human carcinogens, the following scientific approach will be used:

- Mechanistic studies for providing the understanding of the human relevance of identified hazards, such as receptor sub-typing, distribution, species differences, involvement in cell proliferation, nutritional interactions, cellular pathways or 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. Among others, these might include alternative carcinogenicity studies of shorter duration, sub-chronic studies in aged animals, or the 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 receptors such as PPARs would be greatly accelerated;
- The 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 two-year bioassays that may result.

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

2.4.3 Development of *In Silico* Methods

There is a pressing need for the development of *in silico* methods, which should be dealt with immediately the ECDSR becomes operational as an Individual Research Project of Priority, in order to:

- Improve predictivity for endpoints characterised in late non-clinical safety studies, for example chronic target organ toxicity and reproduction toxicity;
- Provide tools to screen and select the best chemical lead at the discovery stage;
- Identify and, if possible avoid, specific structural and activity characteristics linked to safety issues;
- Judge toxico-developability in very early development;
- Help to tailor a specific toxicity testing program.

2.4.4 Intractable Toxicities

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

Intractable toxicities represent issues characterised by the fact that they occur in humans and are currently not well predicted by animal safety testing. On the other hand there, are often findings in non-clinical safety studies for which the relevance in humans is unclear or questionable. Since part of the research (for example drug hypersensitivity) may be initiated from the clinical side working backwards to non-clinical models, the plan is that the safety data warehouse will also play a key role in making this an ECDSR research project *par excellence*. This research project should be initiated when the ECDSR becomes operational. The scope of the project is to:

- Select a few high-impact areas that are currently causing repetitive delays or compound terminations, for example testicular toxicity, biliary hyperplasia or hepatotoxicity, vasculitis, phospholipidosis and hypersensitivity;
- Address the selected issues by, for example, new animal, cellular or other models, human tissues, imaging, fundamental biology and modelling.

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

2.5 Priority Areas for Research in Pharmacovigilance and Risk Management

These have been identified by a multi-disciplinary group of experts including industry, regulators, academia and patient groups as follows:

2.5.1 Optimisation of Data Resources and Strengthening of the Evidence Base

Short-term projects:

- Create an inventory of EU data resources (sources, platforms);
- Create a network of database owners, and initiate a dialogue on quality standards;
- Create an EU academic network of pharmacoepidemiology.

Long-term projects:

- Electronic patient record (technology and standards);
- Data pooling and integration (clinical trial, spontaneous reports, epidemiological, utilisation);
- Extension or creating a network of large population-base automated databases;
- Standardisation of medical and medicinal product data;
- EU data warehouse including, for example, data collected in EudraVigilance database.

2.5.2 Development and Strengthening of Methodologies and Networks

- Strengthening of spontaneous reporting (regional centres, patient reporting);
- Develop signal detection and data mining, including new tools for analysis and prioritising signals, validation of tools and agreements of standards between stakeholders;
- Intensive monitoring of medicines based on clinic, hospital, community or regional centre approaches;
- Develop data sources and methodologies for risk assessment for special medicines (e.g. biologics, vaccines) or special populations (e.g. paediatrics);

- Methodologies for risk minimisation and risk communication to Health Care Professionals (HCPs) and patients, including evaluation of effectiveness;
- Pharmacovigilance-specific ontology.

2.5.3 Development of Novel Methods of Risk Prediction and Benefit–Risk Assessment

- To develop new technologies and methods to better predict safety profiles, based on chemical structure, pharmacogenomics, biosimulation and predictive pharmacology;
- Develop new methods of benefit–risk analysis, including decision analysis tools.

2.5.4 Training and Education

- Identification of training needs for HCPs, and the development of appropriate training programmes in pharmacovigilance and risk management;
- Development and testing of training and education programmes for patients, with priority given to understanding the benefits and risks of medicines.

Other important considerations

The Working Group on pharmacovigilance considered that there are two other important areas that must be considered in the context of the SRA, and the facilitation of resources in this area. First, issues of data privacy and data protection should be considered in such a way that they do not end up obstructing research and innovation. Second, pharmacovigilance research, even when it concentrates on methodologies, cannot be dissociated from looking at individual medicinal products or therapeutic classes. Examples of this are the EU pharmacoepidemiology network proposal, and the proposal for intensive monitoring of medicinal products. The expert group, therefore, cannot exclude such research from the scope of the SRA, even though the emphasis of such proposals would be on methodology rather than specific drug-related issues.

In addition to the priority areas detailed above, the expert working group would strongly support extending the network concept shown in the above section on 'Optimisation of data resources and strengthening of the evidence base' to other areas such as pre-clinical toxicology and mechanistic safety assessment. The working group emphasised that it is important to ensure there is adequate cross-talk between the different networks and different disciplines – there should be a seamless link between all aspects of safety assessment from pre-clinical to post-marketing surveillance. It also stated that the networks and different research areas should be supported by adequate funding.

2.6 Resources

The costs of implementing the safety pillar recommendations are presented in the following table. These costs are estimates per year and will be subject to further refinement as appropriate.

Activity	Costs per year (€mn)
European Center of Drug Safety Research (ECDSR)	36.7
Staff	2.85
Meetings	1.68
Overheads	0.87
Communication	1.0
Education	1.0
Priority Project: Development of in silico methods	7.15
Priority Project: Intractable Toxicities	7.15
3 others Projects	15.0
Biomarker Development	22.5
Project Support	3.0
Project Costs (8 projects)	12.0
Extension of FP6 project	7.5
Relevance of Non-genotoxic Carcinogenicity	22.5
50 Post Docs	7.5
Project Costs (30 studies)	15.0
Clinical Safety and Pharmacovigilance	68.7
Data Resource Optimisation / Stronger Evidence Base	22.5
Development and Strengthening of Methodologies and Networks	22.5
Novel Methods' Development for Risk : Benefit Assessment	11.8
Communication / Education of Health Care Professionals and patients	11.9
IT Infrastructure and support	15.0
TOTAL (€mn per year)	165.4

2.7 List of Contributors

2.7.1 Non-clinical Safety

Non-clinical Safety			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Dusinska	Maria	DG Research
	Lucaroni	Beatrice	DG Research
	Norstedt	Irene	DG Research
Academia	Caldwell	John	University of Liverpool
	Claude	Jean-Roger	University of Paris
	Dayan	Anthony	University of London
	Descotes	Jacque G.	University of Lyon
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	Grasl-Kraupp	Bettina	University of Vienna
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	Schmid	Beat	Swissmedic
	Silva Lima	Beatriz	INFARMED
	Vamvakas	Spiros	EMA
	van der Laan	Jan Willem	RIVM
Companies, Pharma & SME	Barrow	Paul	MDS
	Boubekeur	Karima	Roche
	Carleer	Jacqueline	Lilly
	Claude	Nancy	Servier
	Dahl	Björn	AstraZeneca
	Forster	Roy	CIT
	Gautier	Jean-Charles	Sanofi-Aventis
	Gerry	Oliver	AstraZeneca
	Grandjean	Nicolas	Novartis
	Guzmán	Antonio	Esteve
	Kramer	Peter	Merk KGaG
	Krebsfaenger	Niels	Schwarz Pharma
	LeBlanc	Bernard	Pfizer
	Locher	Mathias	Micromet
	Mariani	Maurizio	Serono
	Pfannkuch (Chair)	Friedlieb	Roche
	Rattel	Benno	GPC Biotech
	Schweinfurth	Hermann	Schering
	Sims	Jenny	Novartis
	Singer	Thomas	Roche
	Spanhaak	Steven	J&J
	Storgaard	Torben	NovoNordisk
	Trennery	Paul	GSK
Patient Organisations	Newton	Alistair	EFNA
Others	Holsapple	Michael	ILSI/HESI
	Vericat	Joan Albert	IVTIP

2.7.2 Pharmacovigilance and Risk Management

Pharmacovigilance and Risk Management			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Arlett	Peter	DG Enterprise
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	Norstedt	Irene	DG Research
	Rainer	Bernd-Walter	DG Research
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	Tsinitis (co-Chair)	Panos	EMA
Companies, Pharma & SME	Boubekeur	Karima	Roche
	Danan	Gaby	Sanofi-Aventis
	de Mol	Omer	Genzyme
	Grandjean	Nicolas	Novartis
	Hauben	Manfred	Pfizer
	Lauwers	Ludo	Johnson & Johnson
	McBride	Garth	Schering
	Pfannkuch	Friedlieb	Roche
	Swain (co-Chair)	Elizabeth J.	GSK
Patient Organisations	Georges	Jean	Alzheimer Europe
Others	de Groot	Mark	LAREB
	Persson	Ingemar	MPA
	Vericat	Joan Albert	IVTIP

3 Improved Predictivity of Efficacy Evaluation

3.1 Summary

This chapter describes how academic clinical and pharmaceutical expertise can be brought together to identify the required 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 cancer, brain disorders, inflammatory diseases, diabetes and infectious diseases reviewed the current state of knowledge, and outlined a strategy to address the key bottlenecks in drug discovery. 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 to establish standards, validate imaging biomarkers and develop regional centres of excellence;
- Create disease-specific European Centres for validation of omics-based biomarkers;
- Co-ordinate the development of national patient networks and databases 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 the joint consideration of ethical issues.

Without exception, these common needs would apply equally to other disease areas, and the creation of European-wide networks and centres will form the basis by which the work of the initiative will spread beyond its current confines. It needs to be stressed that the work is, necessarily, pre-competitive from the pharmaceutical industry standpoint and, therefore, cannot concern itself with specific drugs or with issues that relate to the behaviour of individual molecular entities. Therefore, the absence of certain diseases from the scope of the initiative does not in any way imply that research on these will be starved of resource and interest. The initiative is a small part of the total effort invested in biomedical research in Europe, but we expect that this small part, focused as it is on technical and procedural bottlenecks, will have a disproportionately large effect on future success in all disease areas.

3.2 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 the predictability of success by focusing on the relevant bottlenecks in the drug discovery and development value chain (Figure 1). For this purpose, the major bottlenecks have been grouped into four key areas; pharmacology, biomarkers, patient recruitment and regulatory approvals, as illustrated in Figure 21 below.

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 1 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.

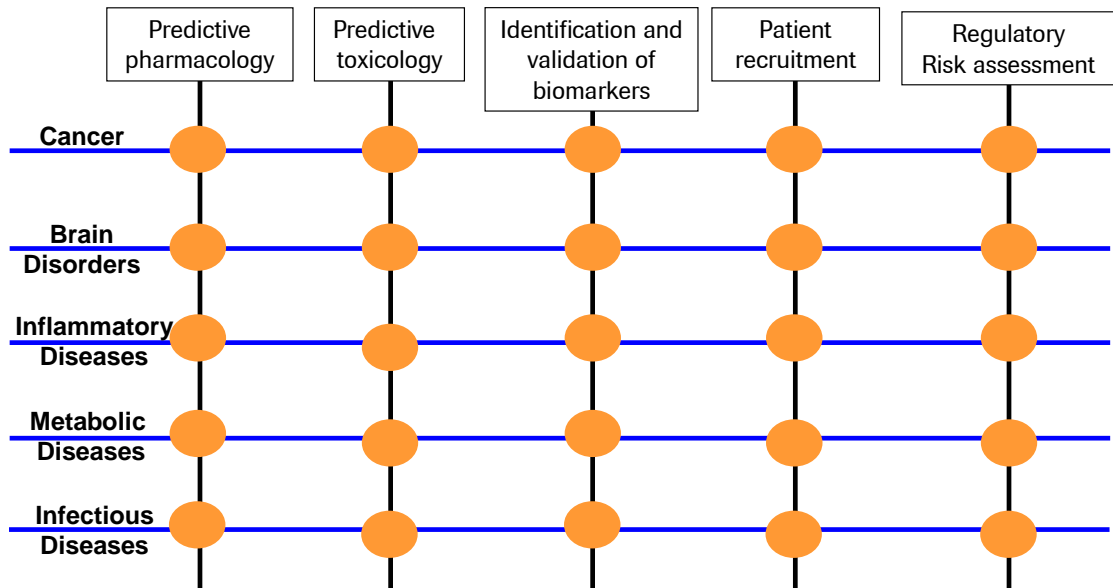


Figure 21 : Efficacy Issues are Often Disease Specific

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

- Cancer;
- Brain disorders;
- Inflammatory diseases;
- Metabolic diseases;
- Infectious diseases.

These diseases have been chosen because they are, primarily, 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. The disease areas were chosen because this Technology Platform provides the opportunity 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 a 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 therapy areas and may also be common to other medical conditions, each disease has a unique combination of issues. In one disease, it might be a lack of predictive animal models in which to test putative treatments. In another, it might be the heterogeneity of the patient population and the inability to recruit the right patient group for clinical trials. In 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 thus 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. It will reduce 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.

3.2.1 Pharmacology

While infectious diseases remain a major threat to the health of Europe's citizens, the challenges to an ageing 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 the disease. Advances in basic science in the past few years have indicated that most common diseases have 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, the basic science of the 1980s and 1990s where single or small numbers of 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 required to facilitate the drug discovery process, and the diagnostic agents needed for early detection of the disease and prediction of treatment responsiveness. Out of this initiative, we will gain an insight into how to prevent disease, but the challenge of discovering disease-predicting biomarkers of sufficient precision and accuracy to justify pre-emptive treatment is considerable. It is inconceivable that such markers would be acceptable, unless firmly based in an understanding of disease mechanisms.

Whether for treatment or for prevention, 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 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 pre-clinical models that are more predictive of efficacy and safety in clinical trials. In order to enhance the predictive ability of pre-clinical 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 medicines 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 pre-clinical 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 pre-clinical 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 medicines and identification of safety biomarkers (confidence in safety) are key enablers to successful translational medicine research in drug development. The technologies and endpoints that most closely reflect those that are, or could be, used in clinical trials should be utilised in order to enhance the predictive ability of pre-clinical models. This will encourage technology transfer in both directions: technologies and biomarkers that are currently used in clinical trials can be more directly adapted to pre-clinical 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, data mining tools and so on. 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.

A 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 critical to the success of modern drug discovery.

3.2.2 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'³⁸. 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 safety, and into disease mechanisms and disease course. They can play multiple roles during the R&D 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

³⁸ Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework,' Clinical Pharm. & Therapeutics, vol. 69, N. 3, March 2001

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 medicines, 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, pre-clinical and clinical information. This will result in better early decision-making, reducing late-stage attrition when the costs are greater.

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 programme 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 efficient healthcare delivery;
- 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 optimisation of biomarker investment, performance and application. 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 current technology to be developed, and access to it improved. 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, for example in blood, urine or cerebrospinal fluid. These would be used for diagnostics, disease progression, prediction of treatment outcome, and measurement of treatment effectiveness.

The other essential technologies are bio-imaging methods such as MRI or PET scanning. 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 in the technologies, such as improvements in resolution, sensitivity and comparability, and a pressing need for greater access for 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.

3.2.3 Patient Recruitment

The next challenge to accelerating the delivery of safe, effective medicines to the market is patient recruitment. There are two key aspects here: 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 lie in the active involvement and collaboration of patients and patient organisations, in the creation of pan-European networks. and in the quality of patient and trial data. In this regard, it will be important to develop clinical research capability and capacity in the new member states.

Clinical trials consume a major proportion of the time required 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 a medicine takes to develop, and will provide a competitive edge in terms of performing clinical trials.

Strategies will be developed with clinicians and patient associations to improve patient recruitment. Consideration should be given to the benefits of advertising for recruitment into clinical trials. A potential approach could be through educating patients about the benefits of participating in research. Furthermore, patient organisations can be pro-active in the setting up of registries, databanks and/or biobanks to support clinical research. Therefore, the early involvement of patient organisations is crucial in the development of strategies towards fast and effective recruitment.

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 proved useful, for example the participation of patient organisations 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 systematic 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.

From the outset, the Innovative Medicines Initiative emphasised the need to involve patients actively in the R&D 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' organisations is the precariousness of their funding. Sponsorship by the pharmaceutical industry lays them open to accusations of bias in favour of their funders, and the possibility of core funding by the Innovative Medicines Initiative for their involvement in innovative therapy development 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.

The causes, clinical manifestation, consequences and treatment of disease and disorders often differ between women, men and children, and the possibility of such differences will therefore be taken into account in the research that is carried out. Partnerships with parent/patient organisations are crucial to address ethical questions and public trust issues in these circumstances.

3.2.4 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 in the post-marketing monitoring processes. In addition, there is an increasing tendency for medicines to be given approval with more restricted indications, with requests for more data if approval is to be given for a broader range of 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, particularly, the EMEA, in a spirit of co-operation and transparency. A detailed list of topics for dis-

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, in order to reduce requests for additional data and regulatory questions following submission. The EMEA Pipeline Project is a welcome opportunity for the industry to work more closely with the EMEA to help expand and improve the range of guidance available in Europe, by sharing the industry's view formed through R&D 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 will add further value. The EMEA's ongoing dialogue with the FDA on harmonising regulatory practices is laudable.
- 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 the quantification of quality-of-life measures. The development of ways to measure drug efficacy beyond the usual primary efficacy end-points is important to prevent potentially valuable medicines 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 the 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 and epidemiological studies that use electronic patient-level data (for example, data from medical records). It is therefore important that databases containing this information are developed and these resources are 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. We envisage that this initiative will assist the EMEA in its efforts to improve risk management, and the measurement of the behaviour of drugs in a real-world setting.
- 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. The 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 (for example, a rolling review) with entry criteria that allow reasonable numbers of products to benefit. The EMEA's responses to the new EU Pharmaceutical Legislation and its Road Map to 2010 already describe grounds for conditional accelerated and compassionate use approvals. The basis is, thus, already in place for discussion on how their current restricted applicability could be widened in the future.
- Develop proposals with the regulators to increase the 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 new treatments, for example calculating statistical power. 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, for example 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 to the variability of such factors as age, gender, disease, and inhibitors of these enzymes. 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. It will also improve 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 22). EMEA's proposal that it will undertake out-comes research using the vast data pool it has available is encouraging in this respect.

- 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 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 to be reassessed, for example the investigation of Bayesian approaches in order to increase the effectiveness of trials, and reduce their size and cost.

Recent announcements by EMEA on transparency, harmonisation of regulatory procedures and improvements to risk management bode well for future co-operation in the regulatory domain. Particularly encouraging are the proposals to include representatives from patient organisations on the EMEA Management Board, and the setting up of scientific advisory working parties (SAWPs) and scientific advisory groups (SAGs). The SAWP of the CHMP provides guidance on the conduct of tests and trials to demonstrate the quality, safety and efficacy of medicines. The SAGs provide independent recommendations to the CHMP on scientific and technical matters in specific therapeutic areas. The aim to provide top quality scientific advice and assessment is an excellent one.

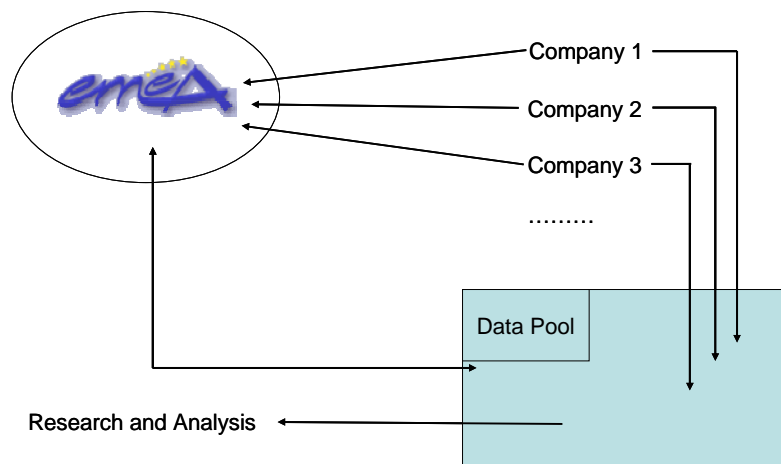


Figure 22 : Potential Data Sharing Model

3.2.5 Rare Diseases and Orphan Drugs

Rare diseases are a diverse group of diseases, which are severe, life-threatening and chronically debilitating. The majority of rare diseases are of genetic origin, and usually prevalent in families. Others comprise rare variants of non-rare disorders. In addition, big footprint diseases, such as cancer, can be broken down in smaller, so-called orphan indications, that affect only a limited number of patients. Thousands of rare diseases are known and, collectively, 20–30 million Europeans are affected, causing a major health problem.

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of life-threatening or very serious illnesses that are rare. This designation is awarded as a result of relatively small numbers of patients and limited market potential. With Europe lagging more than 10 years behind the US in the development of orphan drugs, the European Parliament approved legislation in 1999 aimed at stimulating the development of orphan drugs by providing various incentives to companies. These are:

- Market exclusivity for 10 years;
- Protocol assistance by the CHMP of the EMEA to optimise development plans and clinical trials;
- Access to the centralised procedure for marketing authorization (MAA);
- Fee reductions and access to grants from the EC and member states.

In Europe, the COMP is the dedicated committee within EMEA which reviews and approves applications for orphan drug designation.

In regulatory terms, orphan diseases are defined by a prevalence of fewer than five in 10,000 in the European Union. The incentives now available to companies for the development of orphan medicinal products have created opportunities specifically for biotech companies. Many biotech companies, both

larger international bio-pharmaceutical companies and SMEs, have ongoing R&D programmes for orphan drugs. Only a small number of companies, however, have as yet been able to develop and commercialise products for orphan indications. This is primarily caused by the difficulties encountered for the efficient development of such drugs compared to traditional medicines.

For a heterogeneous group of diseases, the development of diagnostic tools and therapeutic compounds shares a common approach, and is threatened by similar hurdles. For orphan diseases, there are usually no validated and predictive biomarkers. Pre-clinical models are difficult to generate, and large, randomised clinical trials are not possible. Because of the limited availability of patients for enrolment in clinical trials, orphan medicinal products are usually based on limited data, often employing surrogate end-points from clinical trials in small populations. Frequently, marketing authorisations are granted under exceptional circumstances, which require post-approval commitments to perform additional clinical trials. The clinical development of orphan drugs, therefore, requires alternative methodological approaches.

The successful improvement of the R&D process by addressing major bottlenecks in safety and efficacy, as proposed in the SRA, will be directly applicable to the development of orphan drugs. The improvement of predictive pharmacology and toxicology by applying genomics, proteomics and metabonomics technology applications should help address the current safety concerns regarding data obtained from small trials in orphan indications.

The SRA also addresses the improvement of clinical research with regard to efficacy. First, a better understanding of disease mechanisms and the identification and validation of biomarkers should enable translational research in orphan indications, and lead to better pre-clinical models being established. It will also improve clinical outcome trials in small and specific patient populations. Second, the strategies that will be developed to promote the discovery of medicines better adapted to patients' needs should, similarly, be applicable to rare diseases and benefit the development of more orphan drugs. Finally, patient selection and recruitment in trials for orphan drugs may be improved by the development of biomarkers, consultation with patients and patient organisations, and enhanced interactions with regulatory authorities, as proposed in the SRA.

3.2.6 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 databases of the future, to whom the data will be made available, and to understand the IP implications of biomarker data, as well as the ethical and legal issues around patient consent and confidentiality.

3.2.7 List of Contributors

Improved Predictivity of Efficacy Evaluation: Introduction			
Stakeholders Group	Last Name	First Name	Institution
Companies, Pharma & SME	Boubekeur	Karima	Roche
	Incerti	Carlo	Genzyme
	Oskam	Ralph	Genzyme
	Ragan (Chair)	Ian	Lilly
	Strandgaard	Karen	EFPIA
Patient Organisations	Oosterwijk	Cor	European Genetic Alliances' Network (EGAN)

3.3 Cancer

3.3.1 Summary

More than two 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. There are multiple research and clinical networks in Europe, and the success of this proposal is dependent on close working relationships with major cancer organisations such as the EORTC, other national cancer bodies and the major cancer charities.

Our rapidly expanding understanding of the genetics and molecular pathology of cancer development and progression offers a tremendous opportunity for exploiting the underlying science into safe and effective new therapies. Increased understanding of the molecular genetics of cancer development and progression has unearthed a wide array of genetic abnormalities in many cancers. These are potential novel targets, although relatively few of these may be critical to the cancer's growth and survival. Therefore, greater understanding and validation of these targets is urgently required.

This proposal does not specifically address the identification of novel targets, but stem cell research may be valuable in this regard. Improving our understanding of the validity of the multitude of novel targets will enable us to focus rapidly on leads where there is a higher chance of success. Approximately 45% 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 presents 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

- Establishing a core Cancer Biomarker Community of Experts (CoE) with responsibility for the definition of standards, and to outline the plan for the Regional Biomarker Centres;
- The creation of Regional Biomarker Centres (4-6 required) to service populations of 50-60 mn, handling and processing in the region of 50,000 samples annually, using a broad range of technologies, to defined protocols and standards;
- The development of databases of genetics and cancer biomarkers to collect and collate all scientific and clinical data from relevant trials, to underpin the validation process;
- Establishing an expert panel focussed on the paradigm of biomarker development and evaluation;
- Molecular pathology CoE to underpin the biomarker programme and to develop standards for molecular pathology biomarkers linked to clinical and laboratory best practice standards;
- Establishing a Clinical Imaging CoE to link with ongoing FP6 activities in the area of imaging biomarkers;
- Linking of industry, SMEs and academic centres for the development of translational research programmes through an extended Community of Experts in Translational Science.

Pre-Clinical Pharmacology

- The development of novel predictive *in vitro* and *in vivo* models focused on targeted approaches and biopharmaceuticals;
- Establishing a Cancer Stem Cell CoE and research programmes in various cancer types;
- The development of a web-based Clinical Pharmacology CoE, and also research programmes to exploit microdosing approaches, and modelling and simulation techniques;
- Establishing a Systems Biology Cancer Specific CoE, and research programmes focused on cancer prevention, invasion and metastasis, and pulmonary diseases.

Patient Recruitment and Risk Assessment

- The development of a pan-European Cancer Trials Website linked to the WHO-led International Clinical Trials Registry Platform (ICTRP);
- The creation of a European Research Centre for Uncommon Cancers;

- Establishing a European Stakeholder Consortium to enhance our understanding of Value Demonstration in evaluation of novel anti-cancer therapies;
- The formation of a forum with regulatory authorities to discuss such issues as innovative adaptive trial designs, the use of biomarkers, and the review of clinical end-points for regulatory approval.

The proposed programme will generate large quantities of data from a variety of sources. Creating the capacity to search, query, extract, integrate and share data in a scientifically consistent manner across these sources (clinical and scientific datasets) will be challenging. Illustrative proposals are given in the Knowledge Management section.

This programme's chances of success will be significantly increased if it is supported by a strong educational programme, such as the one described within the Education section. Establishing 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 careers and patient groups would be essential.

3.3.2 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 cancers varies, all are associated with a loss of cellular growth control. It is a major cause of morbidity and mortality across the world, with more than 1.4 million cases in the US in 2005, with a similar incidence across the EU-15, with almost two mn cases. In Western society, approximately one in every four deaths is from cancer. Unfortunately, survival rates in Europe for the common cancers remain inferior to the US, with almost one million deaths per year (Figure 23). These figures do not include diagnoses of *in situ* (preinvasive) cancer, or the estimated one million cases of non-melanomatous skin cancer that will be diagnosed in 2005.

Cancer	Cases	Crude	ASR (E)	ASR (W)	Deaths	Crude	ASR (E)	ASR (W)
Oral cavity and pharynx	53,556	14.29	12.71	9.28	20,178	5.38	4.64	3.31
Oesophagus	24,812	6.62	5.38	3.71	22,917	6.11	4.85	3.29
Stomach	70,798	18.89	14.13	9.35	54,919	14.65	10.58	6.81
Colon/Rectum	217,526	58.04	44.04	29.36	111,781	29.82	21.38	13.63
Liver	31,057	8.29	6.41	4.37	34,132	9.11	6.81	4.51
Pancreas	41,340	11.03	8.35	5.53	45,599	12.17	9.02	5.88
Larynx	23,304	6.22	5.45	3.92	10,326	2.75	2.28	1.59
Lung	196,836	52.52	42.16	29.12	183,653	49	38.27	25.96
Melanoma of skin	38,213	10.2	8.89	6.81	9,010	2.4	1.94	1.37
Breast	210,631	56.2	48.84	35.38	73,592	19.63	15.57	10.61
Cervix uteri	22,618	6.03	5.35	4.15	10,098	2.69	2.17	1.52
Corpus uteri	37,411	9.98	8.31	5.81	8,998	2.4	1.7	1.08
Ovary etc.	34,468	9.2	7.74	5.6	22,999	6.14	4.78	3.23
Prostate	144,504	38.55	27.77	17.97	56,035	14.95	9.73	5.72
Testis	8,810	2.35	2.25	2.13	641	0.17	0.15	0.13
Bladder	73,132	19.51	14.7	9.78	29,773	7.94	5.44	3.35
Kidney etc.	46,228	12.33	10.1	7.21	22,418	5.98	4.54	3.03
Brain, nervous system	28,866	7.7	6.91	5.66	21,681	5.78	4.97	3.77
Thyroid	16,311	4.35	3.99	3.22	3,245	0.87	0.63	0.41
Non-Hodgkin lymphoma	52,440	13.99	11.5	8.46	25,906	6.91	5.24	3.55
Hodgkin's disease	8,407	2.24	2.13	2.01	2,251	0.6	0.49	0.36
Multiple myeloma	21,426	5.72	4.36	2.92	15,259	4.07	2.93	1.88
Leukaemia	43,518	11.61	9.55	7.52	29,714	7.93	5.97	4.2
All sites but skin	1580,096	421.57	338.83	238.85	929,992	248.12	186.54	123.93

Figure 23 : Cancer Mortality in the EU15

Importantly, cancer does not affect all races equally, either in terms of incidence or outcome. US statistics suggest that African-Americans are more likely to die of cancer than people of any other racial or ethnic group. From 1997 to 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 the incidence of cancer and the associated mortality by public health initiatives such as those designed to improve lifestyles.

The incidence of cancer varies widely in the EU, both between and within tumour types, as a result of factors such as variations in environmental exposure to carcinogens. Figure 24 contains incidence and prevalence figures for cancer across the 'old' EU. The incidence and prevalence of different cancers at five years varies widely between countries, even allowing for the differences in population size. These 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. We are now witnessing significant improvements in cancer outcomes, initially childhood and haematological malignancies. However, more importantly, the cancer burden of the common cancers such as breast and colorectal has increased significantly in EU populations in recent years. Prevalence figures at five years indicate that more than four million people are 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	1,571,351	1,108,845	4,383,216
Austria	32,828	23,349	93,377
Belgium	47,575	35,107	136,267
Denmark	23,666	15,733	61,252
Finland	20,473	15,068	59,867
France	245,662	189,262	760,295
Germany	346,558	243,658	960,318
Greece	36,505	24,139	95,236
Ireland	12,461	8,025	31,216
Italy	264,551	190,746	750,540
Luxembourg	1,683	1,196	4,624
The Netherlands	62,647	47,170	187,560
Portugal	36,588	26,066	104,738
Spain	151,046	106,444	430,202
Sweden	40,066	30,079	121,628
United Kingdom	249,042	152,804	586,096

Figure 24 : Incidence and Prevalence of Cancer Across EU Countries

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

3.3.3 Present Status of the Disease Area

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

Many factors have influenced the recent improvement in survival rates that has been seen with acute cancer treatment. Better health facilities, improvements in organisation of treatment delivery such as the establishment of multidisciplinary care and the introduction of screening programmes, together with an 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 outcomes, as follows:

- Improved quality of local treatment (surgery and radiotherapy) and supportive care, and the use of effective systemic adjuvant therapies, for example in breast and colorectal cancers;
- Introduction of new chemotherapy medicines;
- Development of novel targeted therapies. These include growth factors such as imatinib, trastuzumab, erlotinib, cetuximab and gefitinib, and anti-angiogenesis agents like 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.

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 progress of new potential cancer therapies into the clinic. The bottlenecks to the drug development process in cancer are, in general, similar to other disease areas, with the major problem areas being pre-clinical pharmacology, the identification and validation of biomarkers and patient access issues. However, there are specific issues that are particular to cancer:

- Cancer represents wide range of diseases each with individual biologies and issues;
- Greater understanding of genetics required for all cancers;
- Inter- and intra-tumour heterogeneity is major problem;
- Greater understanding of pathophysiology required for all cancers;
- Improved therapy is considered an unmet need for the majority of adult cancers, particularly for common solid tumours;
- Lack of efficacy is the predominant issue;
- Safety is important, but is currently a 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 are 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). A Network of Excellence, CONTICANET, has also been established as part of FP6 to co-ordinate the research and treatment of connective tissue cancers across the EU.

The links between industry and academia are currently sporadic and uncoordinated and, as a result, full exploitation of the potential synergies has not been achieved. This has resulted in slower, more costly and generally over-regulated processes. The relationship between industry and European regulatory bodies differs to that in the US, and more interaction is needed. Although the scientific-clinical interface in the cancer field is more successful than some other therapeutic areas, development of the translational interface is urgently required. Links with patients, their carers and patient support groups is fundamental to all clinical/scientific groups, whether in academia or industry, and we urgently need to involve them more consistently and effectively in all our scientific and clinical programme designs. The oncology community will significantly benefit from the education and training together with a robust knowledge management approach, for patients and their carers as well as the physician/scientist community.

The EU has, rightly, judged that it is important for patient groups to be actively involved with the planning and operation of research programmes. This will be strongly supported in the cancer arena, where there are many emerging patient groups. This is fundamental to this proposal.

Cancer research and treatment is functionally multi-disciplinary at all stages. This proposal builds on this strength, through the involvement of a broad range of health care professionals, established industrial partners and SMEs. This aspect of the programme will strongly link with the training and education packages.

Within the EU, both the major industrial partners and the SMEs have a substantial potential for growth. The opportunities are enormous, particularly in the cancer field. These developments, however, would also offer significant collateral benefits for 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 and stratification tools;
- Imaging hardware and software for the digital integration of data.

3.3.4 Bottlenecks

3.3.4.1 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 the efficiency of the drug development process for cancer prevention and therapy by enabling rational early go-no go decision-making and reduced risk of attrition at proof-of-concept. This should focus Phase III accrual on agents with a higher chance of success, and reduce patient exposure to ineffective medicines. This will require access to a wide range of normal human and cancerous tissues, which will need strong links with existing biobanks. The development of validated efficacy and safety biomarkers will significantly improve our decision making process in early development by:

- Early identification of proof-of-mechanism and proof-of-principle/concept;
- Identification of sensitive sub-populations, leading to personalised medicine approaches;
- Efficient early identification of unexpected side-effects;
- Early identification of inactive drugs and a reduction in the risk of late stage attrition.

The focus of cancer biomarker research in the past has been on 'simple' or mechanistic biomarkers using standard biochemical and pathological techniques. Increasingly, biomarkers are being developed that use a variety of evolving platform technologies, including genetics, omics, molecular pathology and imaging. This raises many interesting challenges. The identification, standardisation and validation of these biomarkers is fundamental if they are to be effective in drug development and the regulatory process.

These biomarkers can be used at various stages during drug development, including:

- Diagnostic and prognostic markers (cancer specific);
- Patient stratification by genotyping;
- 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 effective biomarkers would dramatically impact on the quality of decision making in cancer drug development and, therefore, is pivotal to this submission, with a number of core proposals:

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

mulation 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;

- The development of a pathology Community of Experts to support the biomarker programme with quality molecular pathology, including digital telepathology, to enable pathology QC/review, along with standardisation for molecular pathology biomarkers;
- Development of a Translational Science Community of Experts to promote standards of translational research and to develop an integrated programme of research;
- Establishment of a Clinical Imaging Community of Experts Programme to link with the pre-clinical EU CoE established via FP6. 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 and microCT, and to develop image analysis and informatics processing solutions. This network will also be responsible for the identification of imaging biomarkers, in the following prioritised areas in particular:
 1. Angiogenesis;
 2. Invasion;
 3. Apoptosis and proliferation;
 4. Correlation of pre-clinical imaging with clinical outcome.

High-throughput technologies such as genomics, proteomics and metabonomics 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 (for example, 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 Pillar, as outlined in this document, is intended to exploit the data generated from these proposals to the full. It is fundamental to both this and the following sub-sections.

3.3.4.2 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 a better understanding of disease, identify new targets and predict responses to therapy using novel candidate medicines. Major areas for development include:

- Establishing a Community of Experts for Predictive Pre-Clinical Models:
 - These models will include *in vitro* stem cell and engineered cell lines, and models of invasion and metastases. These models will include *in vivo* approaches to evaluate novel biopharmaceuticals. 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.
- The development of a web-based European Clinical Pharmacology Modelling and Simulation Community of Experts:
 - Use of *in silico* modelling and simulation in all stages of drug development;
 - Improved study design to address regulatory questions that would minimise patient numbers while protecting safety and ensuring an improved benefit to cost ratio;
 - Increased use of modelling and simulation will aid the understanding of exposure–response relationships with regard to both safety and efficacy. It will also help the understanding of 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-variables likely to confound a trial's outcome. The resulting study designs will be more robust, executed more quickly with fewer

subjects, and also lower numbers of non-responders or adverse events. The resulting clinical programmes will be cheaper, and result in decisions being better informed.

- **Systems Biology: Establishing Cancer Specific Community of Experts:**
 - To develop European expertise in Systems Biology further, with a particular focus on cancer. This will be achieved by building on understanding from the Systems Biology programmes established in FP6 to capture learning and share experience. Furthermore, 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 recommend the establishment of a Community of Experts in Systems Biology. This CoE will facilitate the co-ordination of research between academia and industry, building on existing relationships with the academic centres of excellence active in the field, many of which already focus on aspects of cancer biology. It will also co-ordinate information exchange with other European and national initiatives in this emerging discipline. The CoE would be responsible for outlining research programmes where systems biology approaches would enhance our understanding of 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.

3.3.4.3 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:

- Establishing 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;
- The creation of a Clinical Community of Experts (European Research Centre for Uncommon Cancers) focused on the treatment of uncommon cancers. The aim of this group is to identify rare patient populations in order 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;
- Establishing a European 'Value Demonstration' Consortium to integrate patient-focused quality of life data, patient reported outcomes and burden of disease.

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

3.3.4.4 Risk Activity and Outcome Assessment with Authorities

Adaptive or innovative trial designs for Phase I, II & III, with Phase IV risk management activities for post-marketing activity:

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

3.3.5 Resources

In this section, the estimates of the costs of these recommendations are displayed by project proposal for each bottleneck. The duration of most of the research topics proposed is between five and seven years, and all figures are expressed in millions of 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.

Activities	Costs (€mn)
Identification and Validation of Biomarkers	42.2
Establishment of Biomarker CoE	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 CoE	2.4
Translational Science CoE and Research Programme	2.5
Clinical Imaging CoE and Research Programme (clinical costs)	12.0
Predictive Pharmacology	9.8
Predictive Pharmacology pre-clinical models CoE and Research programmes	2.5
Cancer Stem Cell Programme	5.0
Web based Clin Pharm Mod & Simulation CoE and research programme	1.5
Establishment of Systems Biology (Cancer) CoE	0.8
Patient recruitment and Risk Assessment	14.7
Pan European Cancer Trials Website	1.5
European Research Centre for Uncommon Cancers and research prg.	4.2
Quality-of-Life and Outcomes demonstrating consortium	9.0
TOTAL CANCER (€mn per year)	66.7

3.3.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Cancer			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Kelm	Olaf	DG Research
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3.4 Brain Disorders

3.4.1 Summary

In 2004, brain disorders accounted for a third of the entire disease burden, with a cost in Europe alone of more than €135 bn in direct healthcare 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 the symptomatic treatments that are currently available. The following proposals are suggested as areas where there is a clear need for further research, and where a public–private partnership can have a significant impact:

- The 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, and establishing European standards and networks for the validation of biomarkers;
- The development of model systems that translate to human pathology and are predictive of clinical efficacy. Human material should be used where possible, and better correlation between clinically relevant and experimental endpoints is needed;
- A better understanding of disease mechanisms at a systems level, using human models of psychopathology and determination of drug effects and dosing along with quantitative behavioural and neuroimaging measures;
- Co-ordinating European stroke networks and developing post-injury treatments, with basic research on functional recovery and determination of validated outcome measures for such treatments.

3.4.2 Introduction

The terminology 'Brain and brain-related diseases' used in this document encompasses all fields concerned with the nervous system (central and peripheral including the senses and motor systems) on all levels (from molecules to behaviour), including diseases of the nervous system. Brain disorders account for around 35% of the disease burden in Europe³⁹. 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 were estimated at €368 bn (€135 bn in direct medical costs, of which €13 bn were directly attributable to drug costs)⁴⁰. Psychiatric disorders, excluding dementia, accounted for 62% of all costs, with the remainder accounted for by neurological disorders. The global market for CNS medicines for the 12 months to March 2004 was \$59.6 bn, and it is the second-fastest growing therapeutic area⁴¹. The cost of bringing a new drug to market today is estimated to be greater than \$900 mn, and the chances of bringing a Phase I candidate to market in CNS is considerably lower (by up to three-fold) than other disease areas⁴². Based on incidence costs, burden and an analysis on unmet needs in Europe, the priorities for brain disorders are set out in Figure 25 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

³⁹ Olesen J. and Leonardi M., The Burden of brain diseases in Europe. *Eur. J. Neurol* (2003) 10: 471-477.

⁴⁰ 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*.

⁴¹ IMS Health Retail Drug Monitor March 2004

⁴² Kola and Landis, J., *Nature Reviews Drug Discovery*, (2004) 3, 711-715

Neurology	Cases (M)	/	Costs €bn
Multiple Sclerosis	0.379	/	8.7
Parkinson's	1.158	/	10.7

Psychiatry	Cases (M)	/	Costs €bn
Anxiety	41.41	/	41.4
Affective Disorders	20.87	/	105.6
Addiction	9.194	/	57.2
Psychotic Disorders	3.69	/	35.2

Figure 25 : Brain Diseases Costs and Incidence

3.4.3 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 slow or stop the progression of Alzheimer's disease, and for more effective symptomatic treatments, including medicines with 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 the 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, and it can only be initiated within three hours of the onset of symptoms, and after a CT scan to exclude haemorrhage. This represents around 3% of stroke patients, with a clear benefit being seen in just 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 (alpha and beta), Copaxone and Mitoxantrone, 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.

In **Epilepsy**, several medicines have existed for many years that control seizures in around two-thirds of patients, but none are disease-modifying and many have serious side-effects. Several new antiepileptic drugs (AEDs) have better efficacy and/or better tolerance, but there are still no disease-modifying treatments.

In patients with **Parkinson's**, levo-dopa and dopamine agonists have been used as symptomatic treatments for more than 30 years, but there are still no disease-modifying therapies, and patients become tolerant to existing symptomatic treatments. As a result, the greatest unmet need is for disease modifying treatments.

The mainstays of treatment in Europe for **affective and bipolar disorders** are SSRIs, with a smaller percentage of patients receiving tricyclics or SNRIs. The next five to 10 years will see an increasingly crowded and genericised market. There is a need 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 that are now in development, and by more personalised prescribing, informed by pharmacogenomics.

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

Acute treatment is necessary for all attacks of **migraine**. The triptans are effective and well-tolerated, but few patients achieve complete relief from pain, and many have recurrences. About 10–20% of patients who have frequent attacks need prophylactic drug treatment. The only available drugs are those with another primary indication, they are generally not very effective and have many side-effects. The greatest unmet needs are for an effective migraine-specific prophylactic medication, and for a more effective acute treatment that has no cardiovascular side-effects.

3.4.4 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, these are:

- The identification and validation of pre-symptomatic and surrogate markers for disease progression;
- The development of model systems that translate to human pathology and are predictive of clinical efficacy;
- A 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.

3.4.4.1 Identification and Validation of Pre-symptomatic and Surrogate Markers for Disease Progression

Brain disease addressed	Dementia, stroke, Parkinson's, MS
Scientific approach	<ul style="list-style-type: none"> • Genomic, proteomic, and metabolomic (including lipidomic) profiling in human pathology samples and animal tissues; • Functional and structural brain imaging, focus on detection of responders vs. non responders to therapeutic intervention; • Correlation of clinical with experimental data and bioinformatics approaches; • Profiling of responders to specific treatments.
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, SMEs, 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 as yet unvalidated (high risk).
Resource allocation	Based on the AddNeuroMed network for Alzheimer's disease (€15m), we can estimate at least €60 mn over five years if it is extended to four 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.

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

Brain disease addressed	All
Scientific approach	<ul style="list-style-type: none"> • Use of human tissue wherever possible, development of better animal models incorporating human receptors and disease mechanisms; • Generation of complex <i>in vitro</i> models that predict efficacy and aligning 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 (for example zebra fish)

	<p>or drosophila) to express mechanisms relevant to humans;</p> <ul style="list-style-type: none"> • Chemical genetics probes, functional genomics (for example RNAi), pathway modelling, and also modelling of clinically relevant end-points in animal models, for example behavioural measures for stroke; • Integration with a relevant biomarker strategy such as that described above in model systems; • Integration of pharmacogenomic approaches into animal or <i>in vitro</i> models; • Identification of key parameters to select responders to specific therapeutic approaches.
How it addresses the bottlenecks	Better efficacy of pre-clinical candidates, and less attrition as a result of non-human translation. Better target validation technologies will result in less failure because of a lack of human efficacy. Bringing risk forward by integrating biology into the discovery process earlier will reduce failures caused by a 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 needed to identify relevant model end points. Industry, SMEs such as contract research organisations. <i>In vitro</i> 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 as yet unvalidated (high risk).
Resource allocation	Six key areas and 10 diseases @ €2 mn = €120 mn over five years.
Metrics of success	Models that would be validated in the clinic and predict clinical efficacy.

3.4.4.3 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, for example 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. Define contribution of polymorphism at key receptor genes to model's properties. 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. Potential to identify responders via pharmacogenomics of modelled response. Rank performance of NCEs in human models to fast-track promising candidate medicines to patients.
Key players, networks and organisations	Academia (neuroscientists, psychologists, clinical scientists, neurologists, psychiatrists), industry, patients organisations, 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 three major disease areas: €2 mn each (total €60 mn) over five years. Support for a co-ordinating SME: €30 mn over five years.
Metrics of success	Investment in specific projects by the pharmaceutical industry: early Phase I discrimination of multiple candidate medicines leading to go or no-go development decisions.

3.4.4.4 Co-ordination of Clinical Intervention Networks and Research Programmes for Stroke and Development of Post-injury Therapies

Brain disease addressed	Stroke/Trauma
Scientific approach	<ul style="list-style-type: none"> • 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 into post-injury neurobiology including plasticity and neuroregeneration in brain and spinal cord; • Basic research into post-injury neurobiology including plasticity and neuroregeneration in brain and spinal cord; • Basic research in rehabilitation approaches and the scientific basis for efficacy.
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 create 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	Co-ordination of European acute centres will be achieved through specific support actions (€1.25 mn). Research into restorative therapies would require €20 mn for academic groups and around €20 mn for SME participation in the projects. It is estimated that this would support about five strategic research projects (STREPS) over five years.
Metrics of success	Novel treatments for brain-injured patients and validated measures for post-injury recovery. More stroke patients assessed \leq 3 hours.

3.4.5 Resources

The total resources required to implement the current priorities has been estimated at €311.25 mn for a period of five years. This is based on the following assumptions: two to three large integrated projects for the identification of pre-symptomatic and surrogate markers; four or five integrated projects and up to 10 focused strategic projects (STREPS) on the development of more predictive disease models; three integrated projects to develop a better understanding of diseases at systems level in psychiatric disorders, including dementia; one specific support action for co-ordinating stroke networks; and five STREPS focused on research into the 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.

Activities	Costs (€mn)
Identification and validation of presymptomatic and surrogate markers for disease progression	12.0
Development of model systems that translate to human pathology and are predictive of clinical efficacy	24.0
Better Understanding Disease Mechanisms (at Systems Level) for Improved Target Selection	18.0
Co-ordination of Clinical Intervention Networks and Research Programmes for Stroke and Development of Post-injury Therapies	8.25
TOTAL BRAIN (€mn per year)	62.3

3.4.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Brain Disorders			
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Others	Moquin-Pathey	Carole	ESF European Medical Research Council

3.5 Inflammatory Diseases

3.5.1 Summary

Chronic inflammatory diseases such as asthma and osteoarthritis affect one in three people in the developed world. There are many unmet medical needs in this field, not least because many medicines give only symptomatic relief rather than treating the underlying medical condition. This section looks at what needs to be done to improve this situation.

- Identify specific biomarkers (molecular and imaging) for 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;
- Pharmacogenetic analysis of inflammatory disease groups to subtype responders/non-responders (improved efficacy/safety ratio/predictive adverse effect risk);
- Increased research into disease mechanisms to provide for true disease modifying therapeutic opportunities, as distinct from simple symptomatic treatment;
- Earlier and more frequent interactions between academia, industry and regulators to understand the new sciences and technologies, and development of new and better guidelines;
- Faster and better access to therapeutics with high value outcomes in the EU;
- 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;
- Develop better *in vivo*, *ex vivo* and *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, in other words systems simulation versus 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.

3.5.2 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 and osteoarthritis, asthma, inflammatory bowel disease (Crohn's disease and related conditions), multiple sclerosis, chronic obstructive pulmonary disease (COPD) and 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 are affected;
- Tens of billions of euros in annual healthcare costs.

Rapid progress in inflammation science and medicine has led to many new treatments and reduced suffering for millions, but there is much still to be done. Many of the therapies currently available 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.

3.5.3 Present Status of the Disease Area

- Inflammation represents a wide range of diseases with individual needs;
- Early diagnosis is important for all inflammatory diseases;
- The 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;
- A greater understanding of pathophysiology is required:
 - The underpinning science is evolving, for example innate immunity and adaptive immunity, but there is a big gap between immuno-inflammatory pathway analysis and a true understanding of disease pathophysiology;
 - Translational inflammation research still nascent;
 - A lack of understanding of the links between pathophysiology, phenotype, genetic and protein markers and clinical outcomes;

- A lack of understanding of how specific inflammation responses or defects lead to different disease outcomes in various organ systems. What are the common themes within inflammation, and what are the differences that ultimately define the phenotypes?;
- Lack of efficacy is still a key issue;
- Safety is also currently an important issue:
 - A lack of understanding of how specific immunomodulation leads to various outcomes in efficacy, host defence, some predictable and unpredictable events;
- A 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.
- A lack of appropriate and predictive pre-clinical models linking human disease to animal models.

How are we Working?

- Multiple relatively small groups and networks:
 - National;
 - Disease-specific.
- The industry–academia interface is sporadic and unco-ordinated;
- Agreed Pan-European Diagnostic/Treatment Disease Definition & Rx standards are not available or not applied for most inflammatory diseases;
- The relationship with regulators could be enhanced;
- Regulatory guidelines require updating to reflect medical need, disease outcomes and appropriate end-points for clinical trials;
- The scientific–clinical interface requires significant improvement, with a focus on translational science, where bridging will be required;
- The interface between both academia and industry with patients at all levels is inadequate;
- There is a need for education, for physicians, scientists, patients and carers;
- Active patient involvement in programme design is needed;
- Active discussion and participation is needed from payers, healthcare 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

- 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;
- Severe asthma and chronic obstructive pulmonary disease;
- Allergic rhinitis;
- Inflammatory bowel diseases;
- Chronic pain;
- Multiple sclerosis (already discussed in the section on brain disorders);
- Atherosclerosis;
- Transplantation;
- Eczema and psoriasis;
- Nephritis;
- Septic shock;
- Other less common inflammatory diseases, for example alveolitis, systemic lupus erythematosus and connective tissue diseases. Other inflammatory diseases could also benefit from work on the inflammatory disease areas identified above as high priority.

Arthritis

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

Osteoarthritis

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 the middle-aged and the elderly. OA is characterised by the breakdown of the cartilage in the joint, causing the bones to rub against each other. The result is 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 autoimmune disease, such as rheumatoid arthritis or systemic lupus, as it does not affect other organs of the body. At present, there are no disease-modifying medicines on the market for OA. Therapy involves the symptomatic treatment of the 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, OA will clearly become an increasingly large problem and, therefore, an opportunity for the introduction of new disease-modifying medicines. See appendix 8.3 for data on OA.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that affects the lining of the joints, causing pain, swelling and reduced mobility for the patient. The most common age of onset of RA is between 35 and 55. 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, patients bear a heavy disease burden. Work-related disability represents the single largest societal burden associated with RA, surpassing its total treatment costs. Recent prevalence studies and a general ageing 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 death, 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, but it is strongly associated with genetic predisposition. RA therapy as a whole is still some way from reaching an efficacy ceiling. See appendix 8.3 for data on RA.

Asthma

Asthma is a common chronic disorder of the airways, characterised by airway inflammation, airway hyper-responsiveness and airway narrowing. It is reversible, either with treatment or spontaneously. The annual cost of asthma is estimated to be \$16.1 bn in the US and \$16.3 bn in the EU (NHLBI, 2004; ERS, 2004). See appendix 8.3 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 hospitalisation are balanced somewhat by the availability of effective treatments which, 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 medicines. Combined with the high patient population of this chronic disease, the R&D unmet need in asthma creates a 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 characterised by a progressive development of airflow limitation. It 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 most common cause of death in the US, with annual costs estimated to be \$37.2 bn – double that for asthma (NHLBI, 2004). See appendix 8.3 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 medicines 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 damage. Meanwhile, only half of moderate and severe COPD patients reach the desired outcome of symptomatic relief and an improved quality of life, largely as a result of 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 as a result of variations in disease definition, diagnosis criteria and type of population studied. See appendix 8.3 for data on allergic rhinitis.

IBD – Crohn's Disease and Ulcerative Colitis

Crohn's disease (CD) is a chronic inflammation of the intestinal wall, typically affecting its full thickness. 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.

Ulcerative colitis (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 8.3 for epidemiology of the IBD population.

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

Chronic Pain

In general, the management of inflammatory and neuropathic pain is still unsatisfactory with currently available medicines, and many people obtain only partial and temporary relief while experiencing problems with side-effects. The pathophysiology of chronic pain is poorly understood. It 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 develop a better understanding of the pathophysiology of pain, neuronal mechanisms and pain pathways subserving 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 analgesic mechanisms provides an opportunity to move forward to a new way of assessing analgesics, based on an understanding of the mechanisms involved rather than the empirical way in which analgesic development has been driven in the past. The way to move forward clinically is to measure multiple signs and symptoms, not just global measures, to evaluate the natural history, to validate mechanistic hypotheses, and to gain an insight into the mechanisms that operate in individual patients. It must be recognised that laboratory pain models should not only be disease 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 short-term 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 pre-clinical 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 pre-clinical 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 the mechanism of novel drugs to be predicted 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, observing 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;
- Understand the effects of NCEs on locally-released mediators of inflammation using *in vivo* microdialysis;
- Understand the effects of NCEs on first order nociceptive neurons (IAdelta and C-fibres) using evoked potentials;
- Understand the pharmacodynamics of BOLD fMRI signals in key brain regions known to subserve pain signalling in response to induced pain;

- Understand pharmacodynamic changes in putative nociceptive neuromodulators using magnetic resonance spectroscopy (MRS) and LC-MS of appropriate biofluids;
- Integrate 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 back-translate from patients to man to animals;
- Provide objective data to allow early go or no-go decisions on NCEs, particularly for unprecedented approaches;
- Provide information to help dose-set in Phase II 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 well enough understood to allow confident predictions to be made when they are employed in drug development studies.

3.5.4 Bottlenecks

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

- Active patient 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 healthcare burden to society;
- Some common pathways understanding of the biology, for example from smoking, could help the understanding of the pathophysiology of COPD, lung cancer, atherosclerosis, Alzheimer's and so on;
- Other inflammatory diseases could also benefit from work on the identified high-priority inflammatory disease areas;
- Few disease modifying treatments are available in these indications – a critical gap;
- The underpinning science is evolving (for example macrophages, B cells, T cells, target tissues, genetics and, proteomics) but there is a big gap between inflammatory pathway analysis and true understanding of disease pathophysiology.

Patients

Given that the EU has judged it is important that the patient groups should be involved in 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 an enormous healthcare burden in an ageing population.

Professional Groups

The work proposal is itself multidisciplinary, and the overall proposal involves a unique combination of professionals (academics, clinicians), established industries (pharmaceuticals, diagnostics, scanning) and SMEs (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.

Industrial Growth

The established industries and the SMEs already have a substantial potential for growth, based on existing knowledge. However, the opportunities for the development of new areas are enormous, especially for SMEs.

These include, among many others:

- Biomarkers;
- Diagnostics;
- Therapeutics;
- Population screening;
- Education;
- Nanotechnology;

- Imaging hardware optimised for measurements;
- Software for image quantification.

The Rank Order of Importance of the Bottlenecks is:

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

3.5.4.1 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, whether they are responders or non-responders, disease progression and 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 pan-European collaborations. This would improve the competitive position of Europe versus the US and Japan considerably;
- A pan-European database will further aid research into inflammatory disease sub-groups, helping disease profiling;
- Identify and 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 healthcare;
- Identifying academic research centres would 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 national initiatives that already exist, such as the one for MS in Denmark;
- There is a need for an education and training component for clinicians, with protected time for research and trial work.

3.5.4.2 Identification and Validation of Biomarkers

Increasingly, information derived from clinical studies in the field of biomarkers and pharmacogenetics is being used 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 dropped earlier in the development process, thereby reducing the resource burden associated with high rates of late-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 and tissue damage;
- Surrogate markers for drug efficacy and safety;
- Markers of host-defence, risk-benefit evaluation and so on;
- Markers for functional recovery or disease modification;
- Predictive genotyping, although the societal implications of this must be considered;
- Population screening not only, through genetics but also using other technologies that can provide a high degree of specificity and sensitivity;
- **Pharmacogenetic markers** of inflammatory disease groups to subtype responders and non-responders, which should result in improved efficacy and safety ratios, and be predictive of adverse event risks;
- **Pharmacogenetics** (patients, ex: allotype responses to antibodies) – five years:
- Polyomics:

- Some of the emerging omics technologies will be useful in the area of identifying common pathways between apparently different diseases although, in this case, it will be important to establish primary aetiological changes from secondary effector mechanisms. A further use 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, for example 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 under study and the indication is established as germ-line genetic variation is essentially fixed at conception.
- **Imaging:** In monitoring disease progression by techniques such as MRI, the big areas for research are:
 - Bioimaging Centres of Excellence for Inflammatory Disease Groups will support the drug discovery and 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 the PET radiotracer development and image analysis and processing solutions that are necessary for image quantification;
 - Linkage of imaging to monitoring disease activity and progression;
 - Standardisation of bioimaging modalities;
 - Building on Cambridge CoE for OA.

Validation of Biomarkers and Standardisation of Biomarker Assays

The big areas for research are:

- Establishing European standards for the validation of markers;
- Co-ordination of national networks, tissue banks, clinical expertise, SMEs' discovery and pharma;
- Regulatory standards and dialogue for the acceptance of validation.

3.5.4.3 Predictive Pharmacology

The big areas for research are:

- Development of *in vivo* and *in vitro* models 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, plus technologists;
- Training of clinical and basic pharmacologists;
- Proof-of-concept networks in the academic sector;
- Systems approach to understanding disease 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, such as 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 can be achieved:
 - 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 cost-benefit 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:
 - Use 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 nanotechnology as systems integrators to study disease and develop new treatments with high value outcomes.
- The following partners are equally important in achieving this goal:
 - Academics: 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, for example in the fields of IT and genomics;
 - Regulators: to conduct retrospective analyses of the application and establish good practice 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 it has been known that patients with rheumatoid arthritis are far more likely to develop cardiovascular problems as a result of arterial disease, yet only in the past couple of years have we begun to investigate and identify the common mechanisms that underlie the two conditions. Mathematical and textual meta-analyses of the existing (published and proprietary) data can be employed to uncover co-morbidities. A second phase of dedicated investments in collaborative research work with academic epidemiologists could also be considered.

3.5.4.4 Risk Activity and Outcome Assessment with Authorities

The big areas for research are:

- Adaptive and innovative trial designs for Phase I, II and III;
- Bayesian methodology and other statistical techniques (e.g. N of 1 trials) to get an early read-out on efficacy and safety;
- Multidimensional scaling techniques;
- Developing, amending and applying validated quality-of-life and disease activity and severity measures that capture drug efficacy beyond primary end-points used routinely, and which could also predict the patient benefits of potential new therapies;
- Establishing good working practices with authorities early in the process;
- Electronic patient records and electronic data capture technologies.

3.5.5 Resources

Costs for many (but not all) of the individual inflammation efficacy enablers have been estimated, and are summarized in appendix 8.4. Most of the research topics proposed would last between five and seven years. The total cost of undertaking the enablers listed will exceed €300 mn over a period of five 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.

3.5.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Inflammatory Diseases			
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3.6 Metabolic Diseases

3.6.1 Summary

This section sets out proposals developed by key stakeholders to promote pre-competitive research in Europe that will address the bottlenecks that exist in the development of novel therapies for diabetes. This disease was chosen from the vast variety of metabolic diseases as diabetes is associated with a number of other metabolic abnormalities, such as obesity, dyslipidemia and metabolic syndrome. In addition, the prevalence of diabetes is expanding in an exponential manner from the current 150 million to approximately 250 million in the next 15 years. This disease and its complications cause not only human suffering, but it is also a major economic burden for the society. There is a huge unmet medical need for pharmaceutical therapies for the prevention, treatment and cure of diabetes.

The group has identified five major research priorities:

- Develop more predictable *in vitro*, *in vivo* and *in silico* pre-clinical models for diabetes and its complications;
- Identify and validate novel targets in diabetes by discovery research in the pathophysiology of the disease and its complications;
- Identify and validate biomarkers for beta-cell function and loss, for treating both insulin resistance and diabetic complications;
- Characterise subpopulations and patient groups using genomics and biomarkers for focused therapeutic and preventive studies;
- Develop quality-of-life and patient-reported outcome metrics to measure the 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.

3.6.2 Introduction

A multidisciplinary group representing major stakeholders with a broad range of expertise was set up to review the bottlenecks in developing novel therapies for diabetes, and to make proposals for how they should be addressed in a pre-competitive 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 that need to be addressed concerning the prevention and treatment of diabetes and its complications are glucose metabolism, lipid metabolism, obesity and cardiovascular diseases. As there are other programmes that focus on dyslipidaemia, atherosclerosis and obesity, the focus of this proposal is research for the normalisation of glucose metabolism. Some academic networks already exist in Europe for diabetes projects that were funded by FP5 and 6. There is no specific budget from the European Commission for diabetes research, but 'diabetes' is included in both 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 mn).

FP6 First Call

- DIABESITY (IP) project: € 1.7 mn – Drug targets for obesity/TP2D;
- TONECA (CA): € 1.0 mn – Molecular mechanism of beta-cell death;
- IMMIDIAB (SSA): € 0.2 mn – Type II diabetes in immigrant populations in Europe;
- EUROTHYMAIDE (IP): €12.0 mn – Major biological functions of the thymus, with emphasis on auto-immune cell destruction.

FP6 Second Call

- EXGENESIS (IP): €12.5 mn – Effect of physical activity on human health;
- EUGENE2 (NoE) project: € 8.0 mn – Drug targets for obesity/TP2D;
- BETACELLTHERAPY (IP): €11.8 mn – Beta-cell programming for treatment of diabetes;

- MOLPAGE (IP): €12.0 mn – Bio-markers for early diagnosis and identification of people at risk of diabetes and cardiovascular diseases.

FP6 Third Call

- EuroDia (IP): € 9.2 mn – Functional genomics of pancreatic beta-cells, and of tissues involved in control of the endocrine pancreas for prevention and treatment of T2 diabetes;
- HEPADIP (IP): €12.0 mn – Hepatic and adipose tissue and functions in the metabolic syndrome;
- PREDICTIONS (STREP): € 1.8 mn – Identification of biomarkers associated with the risk to develop diabetic nephropathy.

FP6 Fourth Call

Two more projects have been submitted to the 4th call; their respective contracts are currently under negotiation:

- SAVEBETA (STREP) – Utilisation of functional genomics to identify pathways responsible for the reduction of beta-cell mass in diabetes;
- INTERACT (IP) – Interaction of genetics and lifestyle on incidence of Type II diabetes.

3.6.3 Present Status of the Disease Area

Diabetes is an epidemic disease, with 150 million individuals affected around the world; this prevalence is rising exponentially alongside an increase in obesity and a decrease in physical activity. It is estimated that in 10 years' time, the prevalence of diabetes will be 250 million. A majority (90%) of patients have Type II diabetes, characterised by abnormal insulin secretion and insulin resistance. The remaining 10% have Type I diabetes as a consequence of beta-cell loss, and a near total lack of insulin. Recently, there has been an increasing incidence of Type II diabetes, associated with increasing obesity in young age groups. This, again, is probably a result of lifestyle changes. There is also a progressive increase in the prevalence of Type I diabetes in Europe, but the causes for this increase remain unknown.

There is a huge unmet need, and many opportunities to improve diabetes therapy. A majority of diabetic patients on current therapies will develop microvascular complications such as neuropathy, nephropathy and retinopathy. Associated diseases are a life-threatening burden, particularly in Type II diabetes. These include dyslipidaemia, atherosclerosis and other features of metabolic syndrome, leading to problems such as stroke and myocardial infarction. Currently available therapies are not effective enough to normalise glucose and lipid metabolism and thus prevent complications. Although much effort has been made at national level in various European countries to address the problem of diabetes, no significant improvement in glycemic control at the national level has been achieved in Europe or the US during the past couple of decades.

The costs of diabetes are high, both in terms of the human suffering it causes, and the economic burden for the community. In European countries, the diabetes-related direct costs of diagnosis, treatment and care are estimated to be, on average, 5% of total healthcare expenditure. Indirect costs, such as lost productivity resulting from disability or premature death, are about equal to the direct costs.

3.6.4 Bottlenecks

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

- Predictive pharmacology;
- Cell-based and animal models for Type I and Type II diabetes;
- Basic research in the pathophysiology of diabetes and micro- and macrovascular complications;
- Modification of behaviour and lifestyle;
- Identification of biomarkers for beta-cell function, mass and for insulin resistance;
- Validation of the biomarkers *in vivo* and in humans;
- Characterisation of focused patient groups for clinical trials;
- Quality of life.

3.6.4.1 Predictive Pharmacology

3.6.4.1.1 Cell-based and Animal Models for Beta-cell Failure and Insulin Resistance

Scientific approach	<ul style="list-style-type: none"> • 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 and so on), to be introduced and tested in cell models; • Animal models have two steps: first to establish a public database with detailed information on existing models. Second, to develop novel humanised 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 compound predictability and reduces the attrition rate in drug development. Allows proof of concept to be tested in pre-clinical 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 and setting up a common database for existing animal models is easy, but to establish target specific models will be difficult.
Resource allocation	€44 mn.
Metrics of success	Validation with the <i>in vivo</i> models and with human studies.
Generic issues	
Interaction with SRA	Knowledge Management.

3.6.4.1.2 Basic Research in the Pathophysiology of Diabetes and Micro- and Macrovascular Complications

3.6.4.1.2.1 Beta-cell dysfunction and loss

Scientific approach	Molecular signature of functional versus 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 <i>in silico</i> research to discover predictive biomarkers and factors associated with beta-cell dysfunction and loss, and biomarkers for micro- and macro vascular complications. Establish a European Central facility to co-ordinate 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 the information from each experimental model to be maximised.
Key players	Beta-cell Gene Exp. Bank (http://tdbase.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 co-ordination.
Feasibility	Do-able
Resource allocation	€26 mn.
Metrics of success	Novel, druggable targets.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.2.2 *Insulin Resistance*

Scientific approach	Examine molecular mechanisms of inflammation, oxidative stress, endoplasmic 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 biomarkers 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/pressreleases), academy, industry, SMEs, regulators.
Infrastructure needs	Gene databanks, patient databanks.
Feasibility	Do-able, extensive.
Resource allocation	€21 mn.
Metrics of success	Novel targets.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.2.3 *Microvascular Complications (retino-, neuro- and nephropathy)*

Scientific approach	Establish target-specific animal models and biomarkers. Examine the contribution of hyperglycemia through different pathways (advanced glycosylated end-products, polyol pathway, protein kinase C, oxidation by free radicals and so on), genetic background and other factors in the pathophysiology of complications. To find associations and causal relationship, use existing human data basis and bioinformatics for <i>in silico</i> research, and blood and tissues samples for novel assays.
How it addresses the bottlenecks	Provides novel targets and biomarkers. Brings the possibility of reducing the size and duration of clinical trials.
Key players	Industry, academy, patient organisations, data bases from large studies (EURODIAB, UKPDS etc), regulators.
Infrastructure needs	Gene databanks, patient databanks, biomarker centre.
Feasibility	Do-able, extensive.

Resource allocation	€14 mn.
Metrics of success	Validated animal model, novel validated targets, successful proof-of-concept studies in focused patient groups.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.3 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 analyse stored samples from long-term studies to find out associated factors and their potential causal relationship with macrovascular complications. Use novel imaging technologies and biomarkers and personalised medicine (genomics) 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, databases and stored samples from large studies (UKPDS etc), regulators.
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre.
Feasibility	Do-able
Resource allocation	€14 mn
Metrics of success	Validated animal models and biomarkers. Novel targets. Successful short and small proof-of-concept studies.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.1.4 Modification of Behaviour and Lifestyle

Scientific approach	Develop means to intervene on eating and exercise habits. Find biomarkers and genomic information for responding populations, with the goal of finding personalised and preventive interventions.
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 mn.
Metrics of success	Validation of biomarkers, successful proof-of-concept studies.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.2 Identification of Biomarkers for Beta-cell Function, Mass and Insulin Resistance

3.6.4.2.1 Beta-cell Function and Mass

Scientific approach	Identify <i>in vitro</i> and <i>in silico</i> markers which detect early changes (preceding hyperglycaemia) in beta-cell mass in pre-clinical 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 <i>in vivo</i> 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	Do-able, extensive.
Resource allocation	€33 mn.
Metrics of success	Validation in the <i>in vivo</i> models and in clinical studies.
Generic issues	Biomarker centre, imaging centre.
Interaction with SRA	Knowledge management.

3.6.4.2.2 Insulin Resistance

Scientific approach	Identification of factors (<i>in vitro</i> , <i>in silico</i>) to correlate with insulin resistance in whole-body or in specific tissues (muscle, fat, liver), or which can be used as prognostic tools for individuals such as the obese, who are at risk of progressing from insulin resistance to Type II diabetes, and which are reversible with therapy.
How it addresses the bottlenecks	Reduces the size and duration of <i>in vivo</i> and clinical studies.
Key players	As in 2.1.
Infrastructure needs	Patient databases, bioinformatics centre.
Feasibility	Do-able, extensive.
Resource allocation	€27 mn.
Metrics of success	Validation in the <i>in vivo</i> models and clinical studies.
Generic issue	Biomarker centre.
Interaction with SRA	Knowledge management.

3.6.4.2.3 Validation of Biomarkers for Beta-cell function, Mass and Insulin Resistance *in vivo* and in Humans

Scientific approach	<ul style="list-style-type: none"> • Beta-cell. In the first instance, correlate the markers with beta-cell function, mass and morphometry in pre-clinical models. Thereafter, validate the markers in humans with diabetes progression, and with the efficacy of therapeutic approaches; • Insulin resistance. Demonstrate a correlation between the markers and insulin-mediated glucose utilisation in specific tissues (liver, muscle, adipose tissue), and in whole body in pre-clinical models and in humans.
How it addresses the bottlenecks	Validated biomarkers allow reduction in the size and duration of <i>in vivo</i> and clinical studies.
Key players	Industry, academia and regulators.
Infrastructure needs	Patient databases, bioinformatics centre, imaging centre.
Feasibility	Do-able.
Resource allocation	€25 mn.
Metrics of success	Validation.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.4.3 Characterisation of Focused Patient Groups for Clinical Trials.

Scientific approach	Using genomics and biomarkers to characterise European subpopulations prone to diabetes and, in patient groups, those prone to beta-cell loss, insulin resistance and micro- or macrovascular complications.
How it addresses the bottlenecks	Use of pharmacogenomic markers to predict and select responsive patients will help to reduce the size and duration of clinical trials (personalised clinical investigations). It will also allow preventive trials. This, together with patient registers, would offer a great competitive advantage over low-cost countries.
Key players	Patient organisations, academia, industry, SMEs, regulators.
Infrastructure needs	Patient databases, bioinformatics centre.
Feasibility	Difficult: requires novel technologies, and ethical and political agreements.
Resource allocation	€32 mn.
Metrics of success	Tailored medicine.
Generic issues	Gene banks, biomarker centre.
Interaction with SRA	Knowledge management, Education and Training.

3.6.4.4 Quality of Life

Scientific approach	Develop quality-of-life measures that capture drug efficacy beyond primary efficacy endpoints, and which could also predict the 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 and so on).
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	Do-able.
Resource allocation	€12 mn.
Metrics of success	Reduced expenses and lost working days.
Generic issues	
Interaction with SRA	Knowledge management.

3.6.5 Resources

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

Activities	Costs (€mn)
Develop more predictable pre-clinical models (<i>in vitro</i> , <i>in vivo</i> , <i>in silico</i>) for diabetes and its complications	6.3
Identify and validate novel targets in diabetes by discovery research in the pathophysiology of the disease and its complications	13.0
Identify and validate biomarkers for beta-cell function and loss, for insulin resistance and for diabetic complications	12.1
Characterise subpopulations and patient groups using genomics and biomarkers for focused therapeutic and preventive studies	4.6
Develop quality-of-life and health economic metrics to measure impact of novel treatments on daily activities and the economic benefits of novel therapy	1.7
TOTAL DIABETES (€mn per year)	37.7

3.6.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Metabolic Diseases (Diabetes)			
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3.7 Infectious Diseases

We can no longer be complacent that we can control infectious diseases, despite hopes that this would be achieved in the 1970s following the introduction of antibiotics and vaccines. A wake-up call to a neglected problem has been provided by 35 newly discovered infectious diseases during the past 25 years, including HIV, vCJD, Ebola, SARS, West Nile, and more than 190 documented human infections with potentially pandemic influenza viruses. This is the first time in history that so many new infectious diseases have emerged in such a short period of time, and it is common opinion that novel infectious diseases will be emerging with increased frequency during the 21st century. A growing global population, overcrowded cities, increased travel, intensive food production, sexual practices, poverty, global warming, and breakdown of public health measures are some of the reasons behind the emergence of new infectious diseases and their rapid spread across the globe. The SARS epidemic is a perfect example of how geographical distances are no longer a barrier, and a disease born in any part of the globe can become a global threat in a matter of hours. A snapshot of the global infectious diseases situation is given in Figure 26 below.

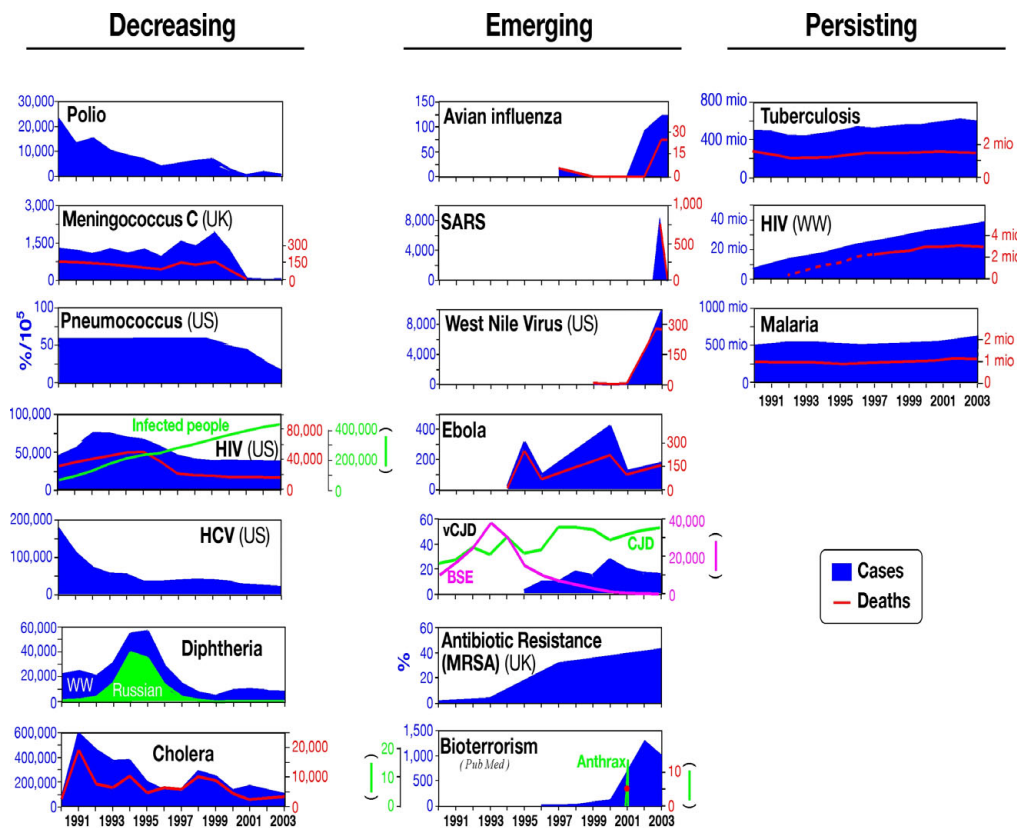


Figure 26 : Global Infectious Diseases Prevalence⁴³

As Figure 26 shows, while progress in controlling many infectious diseases is being made in several countries (left panel), an equivalent number of previously unknown diseases are arising (central panel). Among these, we should take note of the avian influenza, antibiotic resistant bacteria and the bioterrorism threat. Finally, the three major killers—HIV, malaria and tuberculosis—are shown in the panel on the right. Indeed, the population of the developing world faces an enormous burden from infectious and parasitic diseases such as malaria, tuberculosis, visceral leishmaniasis and so on. Over the past few decades, drug development for these diseases has been largely neglected, leaving these countries with serious drug resistance and having to use old and, often, highly toxic drugs. The new funding and philosophical environment has the potential to transform this, and Europe has been at the forefront of the initiatives to develop new medicines for tropical infectious diseases.

⁴³ Rappuoli (2004), From Pasteur to genomics: progress and challenges in infectious diseases. *Nature Medicine* 10:1177-1185.

Europe has recently suffered health challenges and economic setbacks caused by infectious diseases. The bovine spongiform encephalopathy epidemic has shown how devastating infectious diseases can be for the European economy. The present risk of an influenza pandemic, which may cause hundreds of thousands, or even millions, of deaths in Europe, is another example of a likely emergency that we will need to face in the near future. Finally, it should be remembered that more than 15% of all cancers are directly caused by known infectious agents, and that others are likely to be caused by infectious agents that are as yet unknown. Preventing these infectious diseases will avoid millions of cases of cancer. Given the global nature of the infectious diseases problem, Europe does not have the option of sitting still, but must take a leadership role and drive the global agenda for the control of infectious diseases. Securing a world free of infectious diseases is the only way to protect European citizens from the challenge of infections.

Infectious diseases can be controlled in several ways: anti-infective therapy (antibacterial and antiviral agents) and vaccines, with diagnostics critical to both. Additionally, there are certain diseases for which immunotherapy and biopharmaceuticals, such as monoclonal antibodies or immunoglobulin play a critical role.

Vaccines. It is generally agreed that, when available, vaccines are the most effective way to control infectious diseases and to address the problem of multi-drug resistance. In fact, no resistance has ever been reported to vaccines, although in some cases the ecological niche left empty by very successful vaccines like pneumococcus and hepatitis B may be filled, in part, by other serotypes that the vaccine does not cover. Vaccines, a neglected field for several decades, have now gained in popularity thanks to new technologies that make safer products possible.

Antivirals. The past decade has seen a huge increase in the number of antiviral drugs. The driving force for this boom was pressure to contain the HIV pandemic, combined with an increased understanding of the molecular mechanisms of viral life-cycles. This enabled new targets for therapeutic intervention to be identified. There are a number of validated targets for novel antiviral compounds. These include the viral enzymes necessary for the replication of the viral genome, such as the retroviral reverse transcriptases; DNA- and RNA-dependent polymerases and helicases; the proteases necessary for the cleavage of viral polyproteins; and the influenza neuraminidase that is required for the release of the virus from the cell. The availability of validated target enzymes used for high-throughput screening of natural and combinatorial libraries is complemented by an ability to co-crystallise target proteins and their inhibitors, allowing structure-based drug design to be used for the generation and optimisation of more and better leads. Recently, the understanding of the molecular mechanisms of viral entry into host cells has allowed the development of a new class of antiviral compounds, the fusion inhibitors, one of which (enfuvirtide) is already in use for the treatment of AIDS.

Antibacterials. The golden era of antibiotics, which started after the Second World War and contributed to the conquest of many of the infectious diseases, is now over. The widespread use and abuse of antibiotics has created the emerging problem of antibiotic resistance. The new technologies that have thus far been instrumental in the discovery of antivirals, vaccines and diagnostics have been a total failure in the development of new antibiotics against resistant bacteria, despite substantial investment by the pharmaceutical industry. The continuous failures experienced in the field during the past decade have put off many large pharma companies, and during the past decade they have moved away from the field.

Diagnostics. The diagnosis of infectious diseases is essential for prevention, for therapy and for drug development, and it is needed for all applications. However, many infectious diseases are still diagnosed using slow and ineffective methods, if at all.

In conclusion, vaccines, antivirals, antibiotics and diagnostics are all important in the field of infectious diseases. Taking into consideration the fact that vaccines are dealt with elsewhere in the European agenda, the field that is clearly lagging behind and where the science is a real bottleneck is the one of antibiotics and antibiotic resistance, and the availability of appropriate diagnostic tools in the clinic. For this reason, a meeting of experts was convened to identify the bottlenecks in the development of novel antibacterial drugs, and how industry and academia can work together to move the field forward. The following pages report the output of this meeting.

3.7.1 Summary

Until recently, R&D efforts provided new medicines in time to treat bacteria that had become resistant to older antibiotics. That is no longer the case. The potential crisis at hand is the result of the low research success rate, the increasing prevalence of resistant bacteria, and the marked decrease in industry R&D, as well as government inaction. The problems being experienced in antibacterial drug discovery require a co-ordinated and multi-disciplinary response. An expert group representing key stakeholders, such as the pharmaceutical industry, academic institutions, patient representatives, regulators and representatives of

the European Commission identified and prioritised the following pre-clinical and clinical research bottlenecks.

3.7.1.1 Chemistry

Until recently, it was commonly believed that the low success rate in developing new antibiotics derived from the absence of novel targets. However, it was a great disappointment to find that the advent of genomics did not contribute at all to the discovery of novel antibiotics, in spite of the availability of hundreds of novel targets. This has been an eye-opener for the field, which suddenly realised that the problem was not in the targets but in the unique chemical properties required for molecules that need to cross a complex environment such as the bacterial wall, a problem that so far has been solved mostly by complex natural products.

Indeed, the failure of conventional chemistry to deliver novel antibiotics during the past three decades suggests that a new scientific approach is required, where academia and industry can work together. For example, we need to understand why natural products have been more successful than synthetic chemistry in developing new antibiotics. Absence of chemistry dedicated to molecules that have the properties of antibiotics is a major limitation to the development of new antibiotics. It is recommended that the interest of chemists from academia should be stimulated to find synthetic approaches towards antibiotic-like molecules, while maintaining active programs for novel natural products.

As chemistry is a major bottleneck in the development of new antibiotics, it is probable that much of the necessary work will lie outside the scope of IMI. IMI has deliberately been positioned to address enabling technologies rather than molecules in order to avoid moving into areas of direct competition between the pharma partners, and to avoid any possibility of IMI being seen as a direct subsidy of the industry's core business. It is possible that some applications that will be received in the field of antibiotic chemistry will qualify as enabling technologies and meet the criteria for pre-competitiveness as well as other topics in the SRA. However, the creation of natural product-like libraries, for example, rather than the development of underpinning methodologies, should perhaps be topics that could be funded through other modalities within FP7. Based on the input received at the infectious diseases workshop, the recommendation to develop new knowledge using unconventional chemistry approaches is supported, and basic research should be funded through instruments allowing competition between companies. IMI will ensure that all applications received will be checked for their appropriateness to the IMI vision, and redirected if necessary.

3.7.1.2 Diagnostics

The availability of rapid diagnostics, where results are available within 30 minutes without the need for culturing, would be an improvement with respect to recruitment of subjects into trials of treatment for antibiotic-resistant bacteria.

3.7.1.3 Alternative Approaches

In the long term, alternative strategies, for example molecules that interfere with pathogenesis, virulence or Type III secretion, may provide valuable compounds for dealing with bacterial infections.

3.7.1.4 Burden of Disease

Studies that define the burden of disease for antimicrobial resistance are urgently needed. The lack of quantitative outcome measures related to hospitalisation, morbidity and mortality costs for society is probably closely linked to the problem of lack of development of new drugs.

3.7.1.5 Regulatory

Innovative regulatory approaches can be supported by research into clinical trial design, for example by improvement of statistical methods. The potential use of PK/PD studies as the basis for extrapolation between indications should be investigated.

3.7.1.6 Meetings

As a quick win, international meetings should be organised, with the support of the European Commission, to share experiences of the drug discovery process between industry and academia, especially instances where promising molecules were not taken forward or results were surprisingly disappointing.

3.7.1.7 Diseases of the Developing World

Putting aside the lack of a market, there are two key bottlenecks to the discovery and development of medicines for diseases of the developing world:

- There are several targets, but there is a lack of resources to screen for hits on these targets, and subsequently develop these hits into lead and candidate compounds;
- The lack of capabilities and capacities to conduct clinical trials on investigational medicines in the developing world.

Through the IMI, as a focus for pre-competitive collaborative research, additional funding to address these bottlenecks should be sought from philanthropic sources. This funding could be used, for example, to develop targets and leads utilising pharmaceutical industry know-how and expertise. In addition, activities to educate and train clinical trials investigators in the developing world should be progressed.

3.7.2 Introduction

Therapeutically, antibacterials are unusual compared to most other classes of medicines: natural variation within bacterial populations and the eventual emergence of resistance render these agents less efficacious with continued use. New effective antibacterial agents and therapies will, therefore, be needed on a continuing basis. Unfortunately, this new generation of antibacterials has proved extremely difficult to discover and develop. The pipeline of new antibacterials is drying up as the industry has been leaving the field.

3.7.3 Present Status of the Disease Area

Antibacterial resistance has spread globally at an alarming rate, continues to increase, and presents a tremendous global health challenge. Multi-drug resistance has become commonplace in many disease-causing bacteria. Infections that were once easy to treat are becoming problematic and, in some cases, impossible to treat. In consequence, people are suffering severe illness, hospitalisation times are lengthened and mortality increases as a consequence. There is an acute need for novel antibacterials to combat this growing resistance.

A recent analysis published in *Clinical Infectious Diseases (CID)* found only five new antibiotics in the R&D pipeline out of more than 506 medicines in development. By comparison, pharmaceutical companies were developing 67 new drugs for cancer, 33 for inflammation/pain, 34 for metabolic/endocrine disorders, and 32 for pulmonary disease. The CID analysis found that FDA approvals of new antibiotics have declined by 56% during the past 20 years (1998-2002 versus 1983-1987). Since 1998, only 10 new antibiotics have been approved by FDA – only two of which are truly novel, with a new target of action and no cross-resistance with other antibiotics. A growing number of companies with track records in antibiotic R&D appear to be withdrawing from this market: Sanofi-Aventis, Abbott Laboratories, Bristol-Myers Squibb, Eli Lilly and Co., Procter & Gamble, Roche, and Wyeth.

3.7.4 Bottlenecks

In comparison with other therapeutic areas, animal models are quite predictive of clinical outcome in antibiotic R&D. This causes a high attrition rate in pre-clinical research, indicating that the major bottleneck is to bring valuable compounds into clinical trials. Therefore, five key priority areas have been identified by our expert group where there is a need for improvements, and possibilities for productive and successful partnerships.

3.7.4.1 Chemistry

Chemistry is usually not a bottleneck. Traditionally, it deals with molecules and scaffolds, which are of proprietary nature and therefore usually they are not part of the pre-competitive research agenda. In the case of antibiotics, however, it is clear that conventional chemistry approaches have not led to adequate success. In order to make progress, the science of chemistry for antibiotics has to be readdressed. It is a widely recognised fact that for antibiotics to penetrate the bacterial membrane, different chemical properties – often expressed in complex structures – are required in comparison to other drugs. Antibacterials are often derived from natural compounds, which are usually more complex than traditional small molecules and have been naturally selected to interact with bacteria. Furthermore, therapeutic doses of antibacterials are higher than in other indications. For hospital indications, intravenous formulation is essential, and consequently sufficiently high aqueous solubility is a must. Therefore, natural product-like libraries have to be available for successful screening efforts. Such libraries require the concerted effort of

natural product research and synthetic chemistry. In addition, they should be also available to academic institutions to use these molecules in their screening procedures.

3.7.4.2 Diagnostics

The recruitment of patients with antibiotic resistant bacteria is a great limit in performing clinical trials. Rapid diagnostics, taking about half an hour, without a need for culturing would improve the performance of clinical trials.

3.7.4.3 Alternative Approaches

In the long run, alternative approaches to treat infections may offer a valuable tool to cope with the emergence of antibiotic resistance. There is a need for new strategies, which include not just drugs but perhaps biologicals such as phages, enzymes and monoclonals to control bacterial infections. In addition, molecules that interfere with processes relevant to infection could lead to valuable therapies in certain diseases. The basic science for these processes has made substantial progress, while translational research to bring these discoveries to the clinic has been lagging behind. Multi-disciplinary research approaches are necessary to study combinations of different treatment strategies.

One of the recurrent themes of IMI is to close the gap between basic science and early clinical testing. IMI could, therefore, be one of the instruments to progress research in this area.

3.7.4.4 Burden of Disease

Studies that define the burden of disease for antimicrobial resistance are urgently needed. The lack of quantitative outcomes measures related to hospitalisation, morbidity and mortality costs for society is probably closely linked to the problem of the lack of development of new drugs.

3.7.4.5 Regulatory Approaches

Regulatory research into clinical trial design is a prerequisite for innovative regulatory approaches. Both the design of confirmatory clinical trials and the potential use of PK/PD data should be subject to research to optimise costly aspects of drug development. Since current regulation and guidelines from the EU give opportunity for less than comprehensive drug development in areas of medical need, the investigations proposed in this section could provide strategic directions.

3.7.4.6 Meetings

One major bottleneck is the fact that industry and academia do not talk as much as they should, and therefore have totally different ideas of what is needed. With the support of the European Commission, meetings should be organised where results and experiences are exchanged between industry and academia.

Beside these key priority areas, bottlenecks common to all other disease areas were identified:

- Because of the withdrawal of industry from the infectious disease area, a loss of knowledge has taken place. As a consequence, a systematic documentation and knowledge management process is necessary, and should be co-ordinated with the Knowledge Management pillar of IMI;
- Support for professional education and training is needed, and should be co-ordinated with the Education & Training pillar of IMI;
- Research is needed into predictive *in vitro* toxicology and safety tests;
- A harmonisation between EMEA and FDA would reduce requests for additional data. In the case of resistant bacteria, the lack of harmonisation could be an advantage for Europe, because EMEA accepts that the proof of efficacy against susceptible strains may be extrapolated to resistant strains if it is shown that the new mode of action covers the resistant strains;
- The acceptance of limited toxicology and surrogate clinical end-points by the regulatory authorities should facilitate non-clinical and clinical drug development. In acute bacterial infections, the use of surrogate markers is a challenge.

3.7.5 Resources

The total cost of these recommendations (€10 mn) are yearly estimates, and will be subject to further analysis as appropriate.

Activities	Cost per year (€mn)
Diagnostics	2
Alternative approaches	5
Burden of disease	2
Meetings	1
Total Infectious Diseases (€mn per year)	10

3.7.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Infectious Diseases			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Lonroth	Anna	DG Research
	Rainer	Bernd-Walter	DG Research
Academia	Hryniewicz	Waleria	National Institute of Public Health
	Moxon	Richard	Oxford University
	Normark	Staffan	Karolinska Institute
	Norrby	S. Ragnar	Swedish Institute for Infectious Disease Control
Regulatory Authorities	Aronsson	Bo	EMA
	Powell	Mair	MHRA
Companies, Pharma & SME	Dirach	Jorgen	NovoNordisk
	Donadio	Stefano	KtedoGen
	Endermann	Rainer	Bayer
	Felton	Mark	GSK
	Fraisse	Laurent	Sanofi-Aventis
	Labischinski	Harald	Combinature Biopharm
	Ragan	Ian	Eli Lilly
	Rappuoli (Chair)	Rino	Novartis Vaccines
Patient Organisations	Dedes	Nikos	European AIDS Treatment Group

4 Knowledge Management

4.1 Summary

IMI aims to boost Europe's biomedical R&D base by improving the predictability of safety and efficacy evaluation during the drug development process. The Knowledge Management (KM) pillar is an essential component of IMI that provides the data-pooling and data processing infrastructure to support IMI public-private collaborations in Europe.

The IMI Safety and Efficacy pillars, through a process of calls for proposals and project evaluation, selection and funding, will initiate and manage a number of biomedical research projects and communities of experts. The IMI Knowledge Management pillar supports the Safety and Efficacy projects and communities of experts with their information management and information sharing, modelling and simulation tasks.

The recommendations concerning IMI Knowledge Management are:

Set-up a **Translational KM** team to co-ordinate and provide the support to the Safety and Efficacy projects, both during the preparation of calls and during project execution.

KM Translational support to the Safety and Efficacy projects can be summarised as follows:

- Expertise in bridging the safety, efficacy and knowledge management scientific worlds, expertise in data and systems integration technologies, awareness of international and EU projects in the IMI related areas, be proactive in engaging with the IMI project organisation, capable of scoping a domain of knowledge and laying out the current state of the art;
- Effective interfacing of knowledge and skills in a number of domains that recur in the Safety-pharmacovigilance and Efficacy pillars, such as molecular imaging, tissue/bio banking, Health Information Technology (HIT) and Electronic Health Records (EHR), bioinformatics, biomarker databases and systems biology.

Set-up a **KM Platform** team that conceives the overall architecture and delivers an integrated biomedical data platform and interactive scientific exploration tools.

The KM Platform is an integrative tool that assures synergies with management and exploitation of research results by bringing data together in an open and consistent format that is suitable for overall data analysis. The creation of such a platform can lead to new biopharmaceutical insight through extensive data sharing.

The KM Platform team will publish project calls that address the development of components of the KM Platform that are currently lacking or that need specific biomedical extensions. The evolving KM Platform will, over time, trigger and support new types of joint project that exploit the availability of new IMI data.

The scientific and functional requirements for the KM Platform can be summarised as follows:

- Data federation: seamless search and navigation across heterogeneous data sources, both private and public;
- Data integration: the capacity to pool data from heterogeneous sources in a scientifically, semantically and mathematically consistent manner for further computation;
- Shared services: the development, sharing and integration of relevant and powerful data exploitation tools such as modelling and simulation.

The requirements can be met using a distributed/federated, multi-layer, service oriented, and ontology-driven architecture. However, severe gaps were identified in the area of data representation and exchange standards, ontology development, data protection, and text mining. A set of generic R&D projects is proposed in order to bridge these gaps and meet the requirements:

- Set-up a Specific Content Action to evaluate and propose approaches for building the core KM Platform backbone information architecture / ontology that copes with a.o. pharmaceutical assay data;
- Joint public-private collaboration-led development of IMI KM Platform missing components. Examples are:
 - Enhanced standards for data protection in a scientific web services environment;
 - Models and modules for exposing web services (semantics), scientific services and the properties of data sources so that they can be used or transformed in a semantically, mathematically, and scientifically consistent manner;
 - Knowledge-representation models and data exchange standards for complex systems;

- Domain-specific ontologies for the more detailed level of scientific data and types of relationships between data elements needed by IMI;
- Extensions to the best text mining tools, such as Biomint and e-Biosci, for capturing implicit information about complex processes, as described in patents and the literature;
- Innovative and powerful data exploitation tools, for example multi-scale modelling and simulation, considering and integrating from the molecular to the systems biology level and from the organ to the living organism level;
- Build the core KM Platform database of validated experimental data extracted from the literature and from Safety and Efficacy projects;
- An expert tool (ontology/schema/rules negotiator, services/data negotiator) to guide users through the complexities of the data, data models, simulation and modelling tools and so on in a federated environment.

In addition, from an organisation point of view, the KM Pillar should include:

- An advisory Science Panel that supports the KM teams in applied information technology matters, the ongoing evaluation of the state of the art, and the identification of complementary and synergistic technology R&D proposals. The members have a proven track record in understanding the needs of modern biopharmaceuticals, and in applying information technology to these emerging areas of science;
- One or more task forces to investigate and report on cross-disciplinary aspects (for example modelling and simulation of physio-pathological processes), validate specifications, and align priorities;
- A cross-disciplinary task force to review issues (legal, regulatory, security and data protection (see 4.2.1), ethical, intellectual property) related to data sharing, and propose guidelines and specifications for implementation.

4.2 Introduction

4.2.1 Understanding the Challenge

Figure 27 positions the IMI KM Pillar in the wider context of the interplay between biology, pharmacology, and medicine. The advent of molecular biology as the major driver for medicinal therapy innovation has brought about the fusion of disciplines, resulting in high levels of complexity. At the interfaces, new disciplines arise, such as:

- **Genomics medicine** using personalised medicine, pharmacogenomics, the integration of genomic testing data into electronic health records and into diagnostic and therapeutic decision support tools, for example. These topics are discussed at the EU level by the BioMedical Informatics initiative from the European Commission, Directorate General Information Society;
- **Translational medicine** using biobanks, toxicoepidemiology, secondary uses of anonymised patient data pools, integrating clinical trial systems with electronic health records (EHR), genomics enabled pharmacovigilance, and so on;
- **Biopharmaceutical R&D** using target and biomarker identification and elucidation, toxicogenomics, predictive safety and efficacy, systems biology, experimental medicine, traditional assay and omics assay data integration supporting integrated modelling, simulation and drug candidate decision making, and so on.

The IMI KM teams support IMI work in all three areas defined above. Moreover, a core set of common terminology, ontology, data interoperability arrangements and the like is gradually building up as stakeholders are increasingly willing to align with defined interoperability requirements. The Knowledge Management teams will support the Safety and Efficacy teams with their data interoperability needs. As a matter of policy, the KM teams will identify those initiatives and standards that shape the common core, and will recommend their use and point out collaboration opportunities.

In this model of the fusion of disciplines, it appears that data cross borders frequently. Effective security and data protection methods and practices are, however, a condition *sine qua non* for that to happen. When patient data are involved, as is the case in areas such as pharmacovigilance, data pooling from electronic health records and biobanks, the strictest safeguards must apply. The data handling and data sharing in IMI projects will be subject to mandated and audited policies and guidelines derived from best practice evaluation. How to implement these in advanced technologies may have to be the subject of further technical research and development.

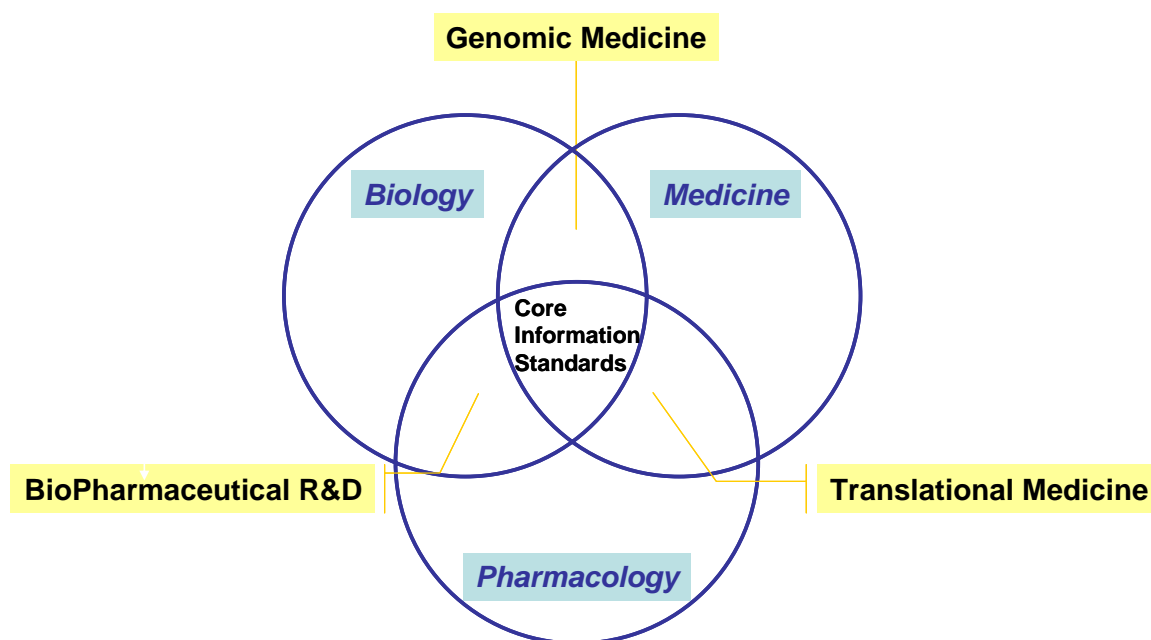


Figure 27 : Positioning the IMI Knowledge Management

4.2.2 Addressing the Challenge

The expert team responsible for creating this section of the IMI Strategic Research Agenda performed an analysis of the IMI scientific and functional requirements, with a series of workshops held in Brussels and Oxford. They discussed current and emerging technologies capable of supporting those requirements, including infrastructure, data resources, data representation and exchange standards, and ontologies. They discussed the nature of the KM services that would be most supportive to the scientific and functional needs of the IMI Safety and Efficacy pillars.

The proposal is to establish a Knowledge Management Implementation body within the IMI Executive Office, composed of two teams. One, Translational KM, will focus on supporting the Safety and Efficacy research projects. The other, KM Platform, will focus on delivering the over-arching integration platform.

The **Translational KM team** will co-ordinate and provide the support to Safety and Efficacy projects during both the preparation of calls and project execution. It will define standards of compatibility across the Safety and Efficacy projects, will promote the sharing of suitable KM technology, and will provide the bi-directional context for Knowledge Management technology R&D, in other words providing a bridge function to the KM Platform team defined below.

The **KM Platform team** will conceive the overall architecture for an integrating biomedical sciences platform, and will research and develop the missing pieces of functionality necessary for data pooling and scientific modelling. It prototypes and tests the evolving platform functionality, and provides the necessary infrastructure. The KM Platform will bring together multi-scale biomedical data on demand for specific biomedical data mining, educational, and modelling purposes relevant to IMI.

This flexible organisation of IMI Knowledge Management activities assures both close support for the Safety & Efficacy scientific projects and the well-co-ordinated implementation of the KM data sharing and modelling and simulation strategy.

At the IMI Executive Office level, the management team includes the leaders of the other three IMI pillars. That Executive Office management team will provide high-level co-ordination, attention for cross-disciplinary aspects, cross-validate project call level documentation, and align and synchronise activities to focus on priorities. These Executive Office management team interactions assure that the IMI IT infrastructure is properly dimensioned, and its functionality closely aligned with the business needs, the scientific requirements and with the priorities of the Innovative Medicines Initiative.

On demand, the KM Science Panel advises the Knowledge Management teams on matters related to the technical architecture, the technical merits and clarity of content of the calls for proposals, the most productive time sequence for the development of the various KM Platform components, and the Knowledge Management technologies in general and their applicability to the biopharma and biomedical sciences.

The responsibilities of the Knowledge Management Implementation body within the Executive Office are to implement the KM SRA.

The Translational KM team will be responsible for:

- Ensuring that the Safety and Efficacy calls for proposals include the opportunities for collaboration with existing KM projects and the information on KM standards;
- Participating in the organisation and evaluation of the Four Pillar project proposals through a quality peer review process, and support the process of arriving at recommendations for project funding;
- Establishing and maintaining a network of expertise in the application of informatics to the needs of predictive safety and efficacy. Building and maintaining an inventory of expertise, methodologies, education and training;
- Providing leadership to Education and Training in the area of biomedical knowledge management talent development;
- Identifying opportunities and managing the exploitation of the databases and the KM Platform.

The KM Platform team will be responsible for:

- Developing and submitting the KM Platform calls for proposals through a consultative process;
- Managing the KM Platform evaluation of proposals and granting of projects;
- Conducting an extensive study of the international and European state of the art prior to the KM Platform calls;
- Managing the KM Platform projects;
- Supervising the organisation and availability of the IMI scientific IT infrastructure.

Figure 28 below illustrates how the Translational KM team will provide this support and play its bridging role.

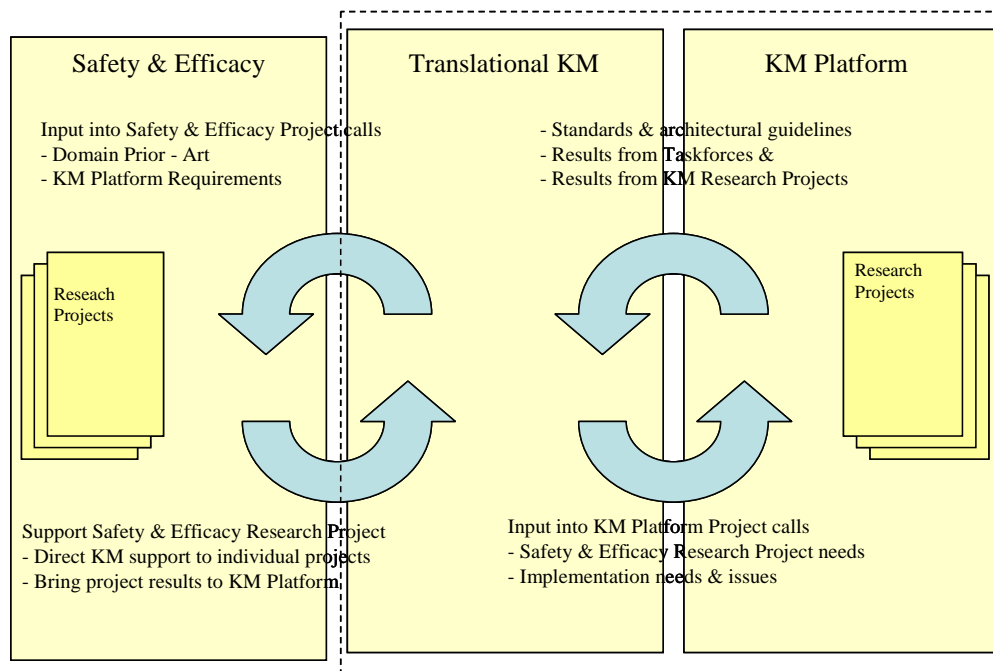


Figure 28 : Knowledge Management Embedding and Bridging

4.3 Translational KM

The Safety and Efficacy research projects will have an information management and data modelling component that is integral to the project and its deliverables. The Translational KM team will support these projects at two different points. First, when the call for proposals is written by documenting the state of the art, by identifying opportunities for leveraging outcomes from existing EU initiatives and specifying the required standards and conventions. Second, during the execution of the project, to ensure project success in implementing the standards and the integration of project results into the Knowledge Management Platform.

It is equally important that specific projects (Safety and Efficacy), with their own IT support, are co-ordinated with the overall KM Platform strategy of IMI and with the evolving capabilities of the KM Platform. It is the task of the Translational KM team to ensure this co-ordination happens.

Each Safety and Efficacy project with an informatics component will fully fund and resource its information management needs. This means that, with respect to the Knowledge Management endeavour, the projects will:

- Fund their IT infrastructure, preferably making use of the KM infrastructure arrangements;
- Fund the IT components, such as gateways, shadow servers, SOA servers and so on, that are required to integrate the project results into the KM Platform;
- Fund the human resources dedicated to the KM team that are needed for the KM liaison function and for integrating their project outcomes into the KM Platform. The number of people involved will vary depending on the complexity of the tasks, as described in the project's programme of work. At a minimum, this should be one FTE.

Examples for Translational KM joint projects are described below. The three examples that follow are taken from this SRA.

4.3.1 Biobanks

The IMI Safety and Efficacy pillars request the availability and integration of biobanks:

- In chapter 2, Improved Predictivity of Drug Safety Evaluation, the organisation of human tissue banks is recommended to address research into intractable toxicities;
- In chapter 3, Improved Predictivity of Efficacy Evaluation, human tissue banks linked to medical records data on phenotypes is considered as a 'must-have' capability. Such banks would serve EU disease-specific regional biomarker centres for the validation of omics based biomarkers;
- In chapter 3, the section on Brain Disorders requests tissue banks for their biomarker work. The section on Inflammatory Diseases requests co-ordinated networks of tissue banks. And in the Diabetes section, biosample banks are requested for biomarkers identification and validation;
- In chapter 3, the section on Cancer, establishing a Systems Biology platform relies on the analysis of tissue samples, body fluids and their data from biobanks;
- In chapter 3, biobanks are also required to couple samples data to medical or clinical data in order to link molecular targets for drug intervention with the pathophysiology of disease, and translate the results of clinical trials into the molecular understanding of the responses;
- In chapter 3, under patient recruitment, the quality of patient data is supported by first-class patient records and biobanks allowing intelligent patient selection, and allowing the investigation of the basis of response and non-response.

A Biobank is a longitudinal and large collection of well-defined and curated biological samples plus the related data including clinical and molecular data. Biobanks feed back into basic research relevant biological samples and their associated pathology data and molecular characterisation data, plus treatment and clinical outcomes data. They are part of the bridge between research and clinical practice, and are an element of the emerging Translational Medicine discipline. They are also addressed in the US NIH Roadmap⁴⁴.

The demand for samples (for example DNA, RNA, proteins, cells, tissue, blood and fluids) is thus increasing for use in high throughput genomics analysis techniques such as sequencing and genotyping, expression analysis. Safety and efficacy sciences require large, centralised repositories to be developed wherein the samples and the data are collected from a network of donating sites, including academic medical centres and community hospitals. An example is the US collaboration to conquer cancer 'C-Change blueprint for a National Biospecimen Network'⁴⁵. The public and private sector must, however, engage in an unprecedented level of collaboration to meet this demand. Bringing together and maintaining diverse samples and their related multiscale data is a real challenge, and will require the use of KM tools for the integration of clinical and biomedical data.

The Translational KM team will support the Safety and Efficacy pillars with timely in-depth state-of-the-art input at the time of writing the calls by identifying complementary or synergistic areas of development. It will provide continuous, effective support to the individual research projects, and also co-ordinate the integration of project data into the overarching KM Platform as required.

Elaborating on the KM support for individual Safety and Efficacy Public–Private Collaborations, one would expect that these projects have expressed, planned and financially resourced needs that the KM team

⁴⁴ <http://nihroadmap.nih.gov>

⁴⁵ <http://www.cchangetogether.org>

can then address with pragmatic best practices to provide ways of setting up or integrating biobanks. This may include the use of existing standards following a minimum dataset approach, biobanks publishing their own ontology and data maps to enable spot integration, and adding unique identifiers to the network, service-oriented architectures and so on.

4.3.2 Healthcare Information Technology and Electronic Health Records

The IMI Strategic Research Agenda puts significant value on the availability of quality electronic health records (EHR) across the EU for the purpose of improved pharmacovigilance and improved clinical trial design.

- In chapter 2, Improved Predictivity of Drug Safety Evaluation, in the Pharmacovigilance section, the creation of an improved clinical trial capacity and capability across the EU is required. In this context, data sources must be enriched with epidemiological, exposure and outcomes data for trials, clinical practice, home care and hospital care. It suggests that there should be technology standardisation in electronic patient records, thus supporting data pooling and integration;
- In chapter 3, Improved Predictivity of Efficacy Evaluation, a pan-EU infrastructure for clinical trials is required to establish an intelligent environment that supports the creation of the electronic patient database of the future. This environment will allow clinical and experimental data to be correlated for the study of biomarkers;
- In chapter 3, to improve patient recruitment, a first-class electronic patient records is required;
- In chapter 3, to improve communication with regulatory authorities, the programme foresees the collection and pooling of benefit–risk data about medicines from patients' medical records;
- In chapter 3, in the Inflammatory Diseases section, a pan-EU database of patients with defined uniform diagnostics, including patient history data, is requested in order to support both research and the development of national patient networks and databases.

The healthcare stakeholders are increasingly willing to align their policies and approaches to health information technology (HIT). In the US, this is exemplified by the Health and Human Services (HHS) Office of the National Co-ordinator for Health Information Technology (ONCHIT). In the EU, eHealth activities are mainly organised through the Directorates General of Information Society, Research, and Health and Consumer Protection. The EU's eHealth Working Group and eHealth Stakeholders Group, which were established in 2005, oversee the implementation of EU eHealth Action Plans. These plans are the result of the i2010 European Information Society programme, and its specific health-related 2005–08 workplan. In addition, the European Commission's FP6 programme supports eHealth and bioinformatics R&D and implementation through the RIDE and Artemis projects.

The eHealth provides a platform for IMI to involve and collaborate with health information technology providers.

An electronic health record (EHR) is a complete set of data across a lifetime about a person's past, current, and prospective health status. It also includes the healthcare that has been provided or is planned. It is stored in a coded, structured, machine-readable form, in multiple jurisdictions and locations, and is accessible in its entirety or in part to legitimate users such as providers, allied health services, emergency services, patients and researchers, from one access point, anywhere and anytime. Patient physiological, clinical laboratory, genomic, environmental factors and treatment and prescription data come together in this virtual file. Provided the necessary safeguards for patient protection and due process (see 4.2.1) are in place, it is an indispensable data source for translational medicine. However, the way that genomic data will be captured in the electronic health record is still an area of research, and one that will be of much interest to the IMI endeavour. How the secondary use of health information data for research purposes will be organised in the future will require a great deal of involvement and attention for privacy and ethical reasons.

Integrating clinical trials, in other words trial protocol driven care, in EHR systems is an area of systems development where the biopharmaceutical industry can bring unique perspectives, needs and expertise to the table, and can take a leadership role. Standards will play a crucial role here too. The CDISC (Clinical Data Interchange Standards Consortium) is a global, vendor-neutral, platform-independent data standard for information systems interoperability. It supports the acquisition, exchange, submission, and archive of electronic clinical data. Participating in its development are global biopharmaceutical companies, technology and service providers, academia, regulatory agencies, and others.

The Translational KM team will assist the Safety and Efficacy pillars with extensive professional networking within the broader EU eHealth community and with state-of-the-art work where the collaboration opportunities have been clearly identified and reflected in the call for proposal documents. The Translational KM team will, equally, actively support the individual Safety and Efficacy Public–Private Collaborations

that have expressed, planned and financially resourced needs with their health information technology integration work.

4.3.3 Biomarker Databases and Data Integration and Analysis

The IMI Strategic Research Agenda requests that an integrated data package standard should be developed to support the acceptance of biomarkers by regulatory authorities in drug filings for new therapies. This requires leveraging data from disparate omics technologies to enable the data to be analysed and mined in integrated and predictive ways:

- In chapter 2, Improved Predictability of Drug Safety Evaluation, this means the creation of a Biopharma data warehouse, with data shared by the pharmaceutical companies about GLP toxicity studies on both new and terminated compounds. The same data warehouse will store the data from the IMI predictive safety research and from any other data sources to support the development of *in silico* models of toxicology that are widely applicable;
- In chapter 2, pharmacovigilance depends on improved data resources – epidemiology, exposure data, outcomes data, medical product data, genomics data and so on – harmonised by a pharmacovigilance ontology and analysed with novel signal detection and data mining tools in order to improve the evidence base and benefit–risk assessment methods;
- In chapter 3, Improved Predictability of Efficacy Evaluation, disease specific biomarker registries and pharmacomedicinal databases are requested to support the biomarker validation work;
- In chapter 4, Knowledge Management recommends building a KM Platform that integrates the validated results from the above-mentioned Safety and Efficacy research activities, and provides the tools to search for and analyse occurrences of a specific scientific interest. The breadth and depth of the KM Platform support the elucidation of additional areas of important research, including the systems biology endeavours.

Systems biology is the quantitative study of biological systems that enables computational analysis of the observations to be carried out⁴⁶. Its goal is the predictive understanding of the whole biology. Systems biology is needed in order to understand biological systems at the predictive level, as required for disease detection, prevention or cure.

The KM Platform described in the next chapter will further the state of the art in this area of large-scale data integration and multiscale modelling and simulation. Many individual safety and efficacy projects will, however, endeavour to develop smaller-scale data compendia and analytical tools that support a specific research need in predictive toxicology or predictive efficacy. These will be supported by the Translational KM team. Examples are the FP6 integrated project in toxicogenomics, CEBS; the FP6 integrated project InnoMed PredTox and the US project OncoMine (cancer transcriptome); and the work being carried out in the EU-funded integrated project BioSim.

4.4 The KM Platform

4.4.1 Introduction

The goal of this chapter is to provide input on the enabling technology – the set of technologies and processes required to process data and information – thus allowing knowledge creation, sharing and reuse. This is required to establish a KM Platform capable of supporting the data- and tool-sharing objectives of the Strategic Research Agenda.

The required flexibility can only be met by a federated, multilayer architecture in which independent components, data sources, scientific services and the like can be configured dynamically and articulated by rules and ontologies. In such a configuration, three areas have been identified as critical:

- Technical infrastructure architecture and services (4.4.4);
- Data sources and properties (4.4.5);
- Knowledge representations and models (4.4.6).

⁴⁶ Zoltan Szallasi, *Systems Modeling in Cellular Biology*, The MIT Press, 2006

4.4.2 Scientific Objectives

Advanced technologies, such as high-throughput screening, genomics, proteomics and metabonomics, have resulted in data generation on a previously unknown scale. Information derived from these data is extensively used in R&D. Examples include target identification and validation, formulation of hypotheses, identification of specific pathways associated with disease states, diagnosis and monitoring. Data integration across heterogeneous data sources and data aggregation across different aspects of the biomedical spectrum, therefore, are at the centre of current biopharmaceutical R&D.

The KM Platform will, ideally, allow:

- Data to be searched, queried, extracted, integrated and shared in a scientifically and semantically consistent manner across heterogeneous sources, both public and proprietary, ranging from chemical structures and omics to clinical trials data;
- Scientific tools such as modelling and simulation to be integrated and shared as modules in a generic framework, and applied to relevant dynamic datasets.

A tool such as the KM Platform can only be successfully conceived, specified, developed and used meaningfully in close collaboration with the Safety and Efficacy pillar projects. The KM pillar organisational approach which will ensure such alignment and collaboration was presented in section 4.2.2 of this document.

The KM Platform's contribution to the previously described examples will be:

Biobanks: The KM Platform could further the state of the art in harmonisation and interoperability by addressing the issues of inconsistent semantics among biobanks within and across organisations. Cooperation between biobanks is very difficult, and there is a major impact on querying for samples – identifying the correct cases and samples across multiple biobanks is not simple. Major data interoperability efforts are thus needed. Examples include NCI CaBIG in oncology, OESO biobank standards, several EU INFSO and RDT projects, and CONTICANET.

Healthcare Information Technology: The KM Platform team can be directed into joint projects, producing integrated patient data from public and private sources, using the IMI KM Platform.

Biomarkers and Data Integration: There is also a huge reservoir of proprietary data, held by both companies and regulatory bodies, on active and discontinued products, as well as marketed products, covering the full scope of R&D. This includes any data from chemical structures to toxicity studies and clinical trial data. These datasets provide invaluable research tools. They could be pooled, possibly supplemented by data extracted from patents and the 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, for example through omics technologies, and the availability of sophisticated mathematical or computational models at the pathway, cellular, organ or disease physiology levels, the 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.

Relevant models are at the centre of all these scientific endeavours. However, the development of multiscale models is a complex task, which is limited by a lack of integrated scientific knowledge. As a result, developing these models can only be undertaken by joint efforts, by the collaboration of scientists from different disciplines, and by goal-oriented and focused initiatives and projects.

The KM Platform addresses this more general need for data integration and aggregation across many heterogeneous data compendia, covering the whole spectrum of biopharma and pharmacomedicinal data, and the need for interlinked modelling and simulation tools that can operate on and co-operate on these datasets. Examples are the Canadian biomolecular interaction network database (BIND), US Pharma GKB database, the EU FP6-funded database BioGRID (microarray data and protein interactions), the EU imaging database MammoGRID (mammography images) and the EU FP6 project GEMSS (grid-enabled Medical Simulation Services).

The terminology 'KM Platform' is used to emphasise the purpose of deriving new knowledge from these data integration and aggregation efforts. The terminology GRID has been used in other publications, emphasising the network computing aspects of such platforms. The meaning of the term GRID has evolved from on-demand high-performance networked computing capacity arrangements such as, for instance, EGEE (Enabling GRID for e-Sciences in Europe), to include the middleware for data integration, data aggregation (Data GRIDs) and the tools for knowledge discovery (Knowledge GRIDs). Examples are the disease specific NCI CaBIG (Cancer Biomedical Informatics GRID) and the proposed EU HealthGRID, BioGrid.

Whatever the terminology, one must address the need for a network computing infrastructure based on internet technology standards for middleware-based semantic interoperability, for multi-scale data representation, and for linking investigative modelling and simulation tools in a scientific workflow: the KM Platform.

Furthermore, it will be important to consider collaborations, to peer review the content model, and to address long-term maintenance by, potentially, involving commercial organisations or public institutions that have experience with the publishing of database resources. This could also be done by setting up a virtual organisation that distributes the work and is committed to the long term.

4.4.3 Technical Objectives

The key technical requirements are:

- Flexibility; in other words modularity (supporting integration of new resources in a standardised way) and configurability (accommodating existing and emerging needs). This is required because:
- The *a priori* scientific and functional requirements are broad and diverse;
- The data resources to be federated by the KM Platform are characterised by a deep heterogeneity in terms of source, ownership, availability, scientific content, quality, level of curation, database design, data organisation, semantics and so on;
- The diverse usage for simulation, modelling and navigation using a variety of methods, some of which are likely to emerge as the result of new R&D;
- The complexity of the underlying science, as well as the complexity of applicable knowledge representation schemas and applicable scientific algorithms;
- Intuitive access to information. From the user's point of view, the knowledge management platform must provide relevant and simple access to information – both in terms of searching and navigation – and to services. It must also provide precise organisation of the content, independent of its source, allow scientifically relevant data integration (data pooling) and data exchange, and provide mechanisms for data capture and annotation. 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 into their day-to-day environments;
- A collaborative environment. It should provide collective working, virtual meetings, knowledge sharing, forums, discussions and so on, which are open to the communities of experts;
- A toolbox for analysis, visualisation, modelling and simulation.

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

In principle, the requirements for the KM Platform can be met by designing a federated environment articulating independent tools, components and resources based on open architectural standards, which is customisable and capable of dynamic reconfiguration.

4.4.4 Solution Component 1: Technical Infrastructure and Services

The KM Platform's requirements are best addressed by a distributed/federated, service-oriented, ontology-driven, layered functional architecture:

- Basic IT infrastructure layer: hardware, operating system software, connectivity network and services such as quality of services, data integrity, firewalls, redundant systems, back-up infrastructure, computer clusters and so on;
- The backbone: services providing basic functionality (data access and security) and interoperability (for example messaging and brokering);
- Data access to heterogeneous resources through a data virtualisation layer (decouple data from their local schema and make data access independent of platform and schema) and a data abstraction layer (provide a common view of all accessible data via a set of ontology / rule-mapping mechanisms);
- Services layer, making application services accessible over the backbone and connecting to data resources;
- Connections layer, providing a secure access point to all authorised users and processes;
- Organisations, describing users and allowing them to share data and services, and collect information.

The most appropriate current technology providing the required flexibility is web services and, in some cases, business-to-business platforms. For handling the scientific tasks in IMI, however, current web service descriptions and annotations must be improved.

Security will have to be addressed at multiple levels:

- Infrastructure;
- Application access;
- Data Protection;
- Access control, which would be policy-governed;
- Privacy-enhancing technology, such as de-identification.

Security and privacy are active areas of research, and technologies are emerging that could be used to ensure the security of the platform. See 4.2.1 on security and data privacy.

The KM Platform will organise necessary and sufficient IT infrastructure services to support the infrastructure that is needed for the Safety and Efficacy projects, as well as to support the KM Platform’s own IT requirements.

In selecting the IT services, the KM Platform team will consider results from several network computing projects, or GRIDs, which were initiated by the current FP6 programme, some of which target eHealth or biomedical science and practice communities throughout the EU.

The functional architecture discussed above is summarised in Figure 29 below:

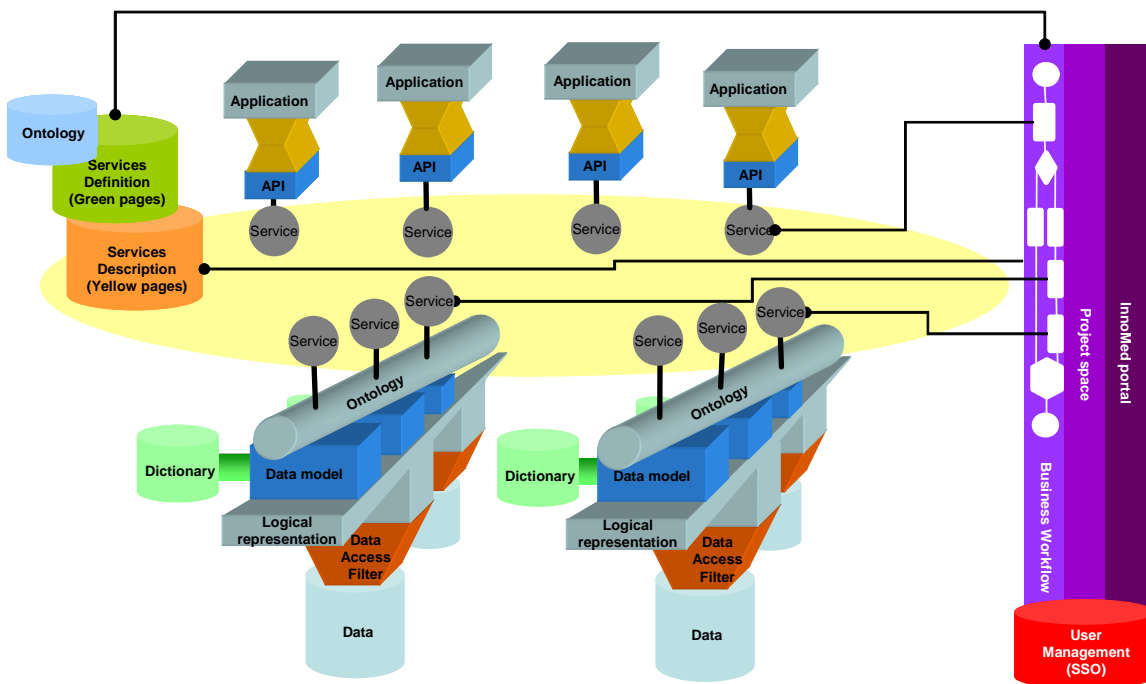


Figure 29 : Knowledge Management Functional Architecture

EU-wide broadband networking is an integral part of the EU’s eHealth vision and programme, and the Commission Services initiated the HealthGRID project. The Knowledge Management team will take that concept into consideration when recommending an IMI IT infrastructure and service provider.

The KM Platform team will develop, maintain and publish an IMI IT computing resources infrastructure that provides guidance for consistency, and it will insist with all parties involved that no money is wasted in duplicative efforts or on incompatible ventures in isolated infrastructure islands. There should be only one IMI Data Centre.

4.4.5 Solution Component 2: Data Resources

The data described by the scientific requirements is heterogeneous. It includes:

- Proprietary experimental data, for example from pharmaceutical companies;
- Highly curated, experimental-quality public domain data, such as SwissProt and PubChem;
- Publicly available, qualitative, documentary data such as Medline, WDI and CAS, sequence databases, and chemical structures database, for example CAS and Beilstein.

Provided it is possible to apply relevant transformations to build composite datasets that are consistent in terms of data content, data quality, data descriptions, and of mathematical properties with the scientific objectives and algorithms to be used, it is possible to assemble useful aggregated datasets.

One requisite is that the implicated data sources should be fully understood: how were the data obtained, for what purpose, what are their quality and validation levels, how complete is the dataset, what the dataset's bias, what are the standard errors of the measurements, what protocols were used, and so on. In the data exchange formats that are currently under development, these aspects are poorly developed. There is no mechanism for creating a virtual experimental data warehouse on the fly. Standard specifications should be developed in the areas of omics and clinical trials.

In addition to issues that relate to the meaning and significance of data discussed above, data sources can differ widely in data curation and the quality control that was applied when they were created. This is a particular issue for pre-clinical experimental data repositories. Data quality is critical, however, and sub-standard data must be eliminated. This requires, at the very least, that recommendations should be developed within IMI, and an index of quality (confidence) be assigned.

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 would probably fail: too many sources, scientific models and algorithms are integrated into the KM Platform. A new type of 'intelligent wizard' will have to be designed.

4.4.6 Solution Component 3: Knowledge Representations

This layer should be based on a set of business entities uniquely defined across IMI data sources and services. This will ensure:

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

By business entities, we mean an aggregate of data (or a representation) that describes some entity (science object) that exists in reality and is relevant to the Innovative Medicines Initiative scope. Examples include a protein, a tissue sample, an assay, a protocol, a domain actor such as a research unit, a person, or even some information resource such as a document or a technical schema. The collection of business entities is governed by an ontology which describes the business entities and their properties, and the relationships between them. The rules that will ensure quality data collections should be crafted by resorting to these ontologies.

Complex business entities can be assembled from a well defined set of elementary business entities. For example, a business entity describing an assay result will probably comprise a compulsory set of elementary business entities describing science objects such as chemical entity, buffer, dilution, molecular target, protocol, species, strain, unit and so on, each with specific types and properties.

Each business entity is assigned logical property attributes, which define how it can be processed, and descriptive attributes, which define what the business entity is about. Together, these logical and descriptive attributes must be sufficient to describe the data element properties fully and unambiguously, to drive the methods that are applied to the data elements, such as calculations, translations, transcoding and transformations, and to search, navigate, explore, filter, and aggregate data.

These representations and ontologies will be used for a variety of purposes, such as searching and mapping data from heterogeneous sources, dataset 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 KM Platform backbone business entity ontology. For the most part, it will have to be developed, taking into account current initiatives, existing standard data representation models, and reference ontologies currently used in the life sciences.

Ontologies used to describe data properties, restrictions and constraints of local data repositories will have to be mapped to the KM Platform backbone business entity ontology. This will require each local data source to expose its local ontologies (and logical schema, rules etc) to the central KM Platform 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 KM Platform core ontology. Similar tools will be required to map the schema of the source database to the data federation tool. The ontology drives an interactive data negotiator articulating data and services. Further developments are needed building on current mediator technology.

4.4.7 Looking for Synergies

Several of the issues addressed above, notably in the area of data integration and semantic interoperability, are the focus of European Communities-funded, 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 the Biomedicine NoE, also focusing on methods for bridging medical informatics and bioinformatics, data interoperability and data mining;
- More generic projects aimed at the wide-scale adoption of semantic technologies, such as the two Knowledge Web NoE and REVERSE;
- 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 organisations, and research efforts should be aligned. Similarly, an inventory of current initiatives on biomedical datasets, representation models, specialised applications, grid computing, semantic grids and the like should be carried out.

4.4.8 Building the KM Platform

The KM Platform is not an end in itself, but a set of tools to advance predictivity in drug safety and efficacy. The KM Platform activities are thus initiated and executed in close collaboration with the Translational KM team and the Safety and Efficacy Public–Private Collaborations. In the preparation phase for the call for proposals, the Translational KM team will contribute with state-of-the-art briefs from which guidance for the prospective Public–Private Collaborations will be derived, and included in the call for proposals documentation. The guidance will cover topics such as current concepts, collaborations to consider, opportunities and standards.

At the most general level, the KM Platform comprises both the infrastructure and multilevel connectivity component, and the toolbox and application component for modelling, simulation and visualisation. The KM Platform advances the state of the art for purposeful multiscale data integration and its scientific exploration, while focusing on predictive safety and predictive efficacy sciences.

4.4.8.1 Specific Content Action

A Specific Content Action will be set up to evaluate and propose approaches for building the core KM Platform backbone information architecture / ontology that can cope with a.o. pharmaceutical assay data. The feasibility and quality of the KM Platform, and ultimately its scientific relevance, relies on high-quality, robust, business-focused, scalable, state-of-the-art ontologies. 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 KM Platform development projects, the Specific Content Action should be set up to evaluate all aspects of information architecture, the needs, the standards, the current research efforts and to evaluate what it would take to built the KM Platform backbone and, possibly, to provide proof of concept. The recommendations will guide further KM Platform components development.

4.4.8.2 KM Platform Development Work

The following topics were identified as areas in need of further R&D:

- Review security and privacy issues, notably in the legal, regulatory, ethical and intellectual property areas, and propose guidelines and specifications for implementation in the context of the KM platform;
- The technology for data protection in a Web Services context is not mature. Standards are still evolving, with implementations often falling behind; examples include SAML and XACML. We suggest these standards should be evolved to the level required for IMI purposes, for example semantic rich annotations of web services for service discovery. See 4.2.1 for security and data protection;
- Scientific knowledge representations: IMI KM Platform will rely in large parts on the availability of high-quality knowledge representation models and data exchange standards, which are presently largely lacking, inconsistent, or incomplete for scientific data. The focus should be on developing knowledge representations approaches for complex systems such as systems biology and disease models, as well as research processes;
- Domain ontologies: the KM Platform backbone ontology as well as some new domain-specific ontologies will have to be developed and built on sound theoretical foundations, taking into account current initiatives, existing standard data representation models, and reference ontologies currently used in life sciences;
- Text and data mining: current information extraction techniques are relatively successful at extracting entities and simple pair-wise relationships between entities, for example protein–protein interactions. While this is extremely useful, more advanced tools are needed to extract the implicit information about complex physiological processes required by computational models;
- Data extraction and curation: the quality of data is of key importance. Data curation efforts undertaken together with the Safety and Efficacy Public–Private Collaborations should aim at building a KM core reference database of validated experimental-quality data integrated from various sources;
- 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. An expert tool for exposing the properties (including scientific properties) of local data sources and mapping them to the KM Platform core is required;
- Data/services negotiator: a black-box approach should be avoided and the scientist must remain in full control of the process at all times. 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 KM Platform data, data models, simulation and modelling tools in a goal-oriented, scientifically relevant and intuitive manner. This includes the development or enhancement of semantic query languages;
- System biology toolbox and framework for assembling and launching composite analytical, simulation and visualisation strategies.

4.5 Resources

The costs realistically estimated for implementing the recommendations described in this chapter are: €14.9 mn per year for a period equal to the initiative's initial duration (2007–13).

The elements considered in calculating the costs for the KM programme are related:

- To establish the Translational KM and KM Platform teams within the Executive Office;
- To establish the Translational KM team with subject matter experts in applying informatics to critical biopharma & biomedical needs areas. The examples given above were biobanks, electronic health records and biomarker databases;
- To establish the KM Platform team with experts in advanced informatics concepts and implementation;
- To establish and operate the technical advisory KM Science Panel.

In addition, resources have been allocated for the IT infrastructure and support in the Safety pillar (€15 mn) and the Efficacy pillar (€21 mn). It is indeed 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. These budgets, therefore, support:

- Safety & Efficacy specific applications development;

- IT hosting by an external vendor, or preferably, through contract with the KM Platform;
- IT costs related to data management within the KM Platform.

In total, €51 mn per year have therefore been allocated to the development and implementation of the Knowledge Management part of this SRA. These bottom-up estimates are of an expected magnitude as the rule of thumb is that 10% of the overall budget must be reserved for information / knowledge management tasks. Further successive refinement of this budget will be undertaken when the priorities are defined, the call for proposals is being written, and the consortium projects reviewed and approved.

In the tables below, costs are shown for the Translational KM participation in joint projects, and for the KM Platform R&D projects. An average yearly cost is calculated from these numbers; however, half of the total costs will be incurred during the first 30 months of the initiative because of immediate infrastructure needs.

For the KM infrastructure costs, the tables below borrow numbers for similar efforts from one of the largest IT Outsourcing Services Provider companies.

4.5.1 Running the KM Teams (Translational KM and KM Platform)

Project support and management	Costs per year (k €)
<ul style="list-style-type: none"> • Eight full time staff + admin loaded costs One Head and seven subject matter experts / project managers 	1,500
<ul style="list-style-type: none"> • Science Panel costs – four meetings, including facilities, and ad hoc consultations 	200
<ul style="list-style-type: none"> • Task Forces (State-of-the-art, best practices, legal / ethical, security and data privacy), three at 130k (five involved, 40 man days, four meetings) 	550
<ul style="list-style-type: none"> • Call for Proposals (expert input, call presentation, peer review, etc.) feedback to Scientific Committee SRA 	300
<ul style="list-style-type: none"> • General support (talent inventory obligations, people networking, contribution to IMI communication, education, prior art studies, conferences, etc.) 	750
Total Project Support and Management	3,300

4.5.2 KM Platform Costs

KM Platform Infrastructure (hardware and software)	
Central gateway - One central site and three distant sites – set-up and running costs	3,700
User software licences	1,800
Development/analytic platforms (licences, applications & development)	2,700
Manage and meet the service provider / application service provider	200
Total Infrastructure and management	8,400

KM Platform Research Projects			
Research Project	Duration (months effective)	Total costs (k €) 7 years	Costs per year (k €)
Platform 'Specific Content Action'	18	2,000	-
KM Platform development	48	8,000	-
Data curation	24	2,500	-
Demonstrator Validation	12	1,500	-
Build final Platform deliverable	12	1,500	-
Total KM Platform Projects		15,500	2,210

4.5.3 Translational KM Costs

In addition to the budgets allocated to KM in Safety, the KM pillar has reserved € 0.98 mn to support joint projects and € 23.7 mn to support Efficacy KM (infrastructure and support).

4.5.4 Summary of Resources Needed

Activities	Costs per year (€mn)
Running the KM Teams	3.3
KM Platform Infrastructure	8.4
KM Platform Research Projects	2.2
Translational KM Joint Projects	1.0
Translational KM Efficacy Support	23.7
TOTAL KM (€mn per year)	38.6

4.6 List of Contributors

Knowledge Management			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Iakovidis	Ilias	DG Information Society
	Norager	Sofie	DG Information Society
	Norstedt	Irene	DG Research
	Rainer	Bernd-Walter	DG Research
Academia	Breton	Vincent	CNRS
	Ceusters	Werner	Unversität Saarland
	De Moor	Georges	University of Gent
	Hofmann	Martin	Frauenhofer Institut
	Legre	Yannick	CNRS
	Sanz	Ferran	Universidad Pompeu Fabra
	Van der Lei	Johan	Erasmus University
Companies, Pharma & SME	Barnes	Julie	BioWisdom
	Boubekour	Karima	Roche
	Boyer	Scott	AstraZeneca
	Claerhout	Brecht	Custodix
	Coupet	Pascale	Temis Group
	French	Dan	Consider Solutions
	Gardner	Steve	BioWisdom
	Grandjean (Chair)	Nicolas	Novartis
	Lave	Thierry	Roche
	Lisacek	Frederique	Genebio/SIB
	Mestres	Jean-Christophe	IBM
	Michel	André	Aureus Pharma
	Peeters	Marc	Roche
	Pegler	Geoffrey	Insightful AG
Vatant	Bernard	Mondeca	
Others	Moquin-Patthey	Carole	ESF – European Medical Research Council

5 Education and Training

5.1 Summary

Based on consultation with stakeholders, the E&T workstream has identified a number of gaps within education & training in support of the medicines development process. A SWOT analysis was 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 the education and training of 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, such as members of research ethics committees, journalists, venture capitalists and patients. To complete the loop, patients should be involved as they 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 system for E&T parallel to 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 to:

- Establish the EMRA, including a central co-ordinating unit and an advisory E&T council;
- Establish programmes for integrated medicines development and for ethics committees and patient organisations;
- Establish programmes for safety sciences, scientists within pharmaceutical R&D and Pharmaceutical Medicine professionals;
- Establish regulatory affairs-based programmes;
- Establish programmes for bio-statisticians, bioinformaticians and biomedical informaticians.

It is proposed to establish the programmes at centres of excellence across Europe. The courses are to be held twice a year. Other activities will be needed in parallel. These include:

- Establishing criteria for centres of excellence and the 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 academics;
- Open dialogue with EU member states on curricula, including establishing European criteria for curricula;
- The development of an accreditation system for E&T;
- Mapping existing Public–Private partnerships in E&T;
- Identifying existing relevant European curricula.

It is important to realise that medicines R&D requires a trans-disciplinary approach, involving many of the traditional scientific areas within life sciences and, in addition, technological areas such as biotechnology, nanotechnology, medical technology and IT.

5.2 Introduction

The objective of this chapter is to describe the gaps that have been identified relating to education and training in the medicines development process. It will also discuss how to bridge these gaps to align with the new tools and requirements of the process to provide new medicines for the benefit of patients, science and society.

Europe has great potential for innovation because of its excellent science, education and training base. However, it is lagging behind because of a lack of adequate funding, insufficient co-ordination of efforts and resources and weak strategic intent, as well as an inability to react with sufficient speed and force to 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 the assessment of safety and efficacy as well as for medical practice. The 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 will also need to be addressed. Furthermore, the consultation with stakeholders during the creation of this SRA revealed a need for people indirectly involved in the medicines R&D process, including patient organisations and the public, to gain an insight into how it operates.

Definition of Education and Training:

In the context of the Innovative Medicines Initiative, Education & Training is defined in the following way:⁴⁷

- 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 2005,⁴⁸ an analysis of the gaps within education & training in support of the medicines development process was carried out. The gaps cover 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 an integrated overview of the entire process, at a variety of levels. For specialised professionals, such as managers, project managers and project team members, it is important that they have an understanding of the interdisciplinary aspects of pharmaceutical R&D, and the requirements of the downstream process towards the availability of the medicine to patients within all three main topics of the regulatory dossier: non-clinical, clinical and quality (CMC⁴⁹). A high level, 'helicopter' view is essential for many stakeholders in the process, for example regulatory authority personnel, clinical investigators, university teachers, ethics committee members and journalists.

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

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

5.3.2 Specific Gaps

The specific gaps that have been identified include:

- The current organisation of universities facilitates the 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;^{50,51}
- 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 industry. A situation where there is a flow of expertise between the three parties will facilitate share and exchange of knowledge;
- Translational science from basic and non-clinical research to the clinical sciences. There is often little or no interaction between clinical scientists and, say, human biologists, even though they may work on the same scientific topics. This gap is critical, and has yet to be bridged. Transla-

⁴⁷ Source Wikipedia, The Free Encyclopedia, <http://www.wikipedia.org>

⁴⁸ Reports from workshops, E&T1, E&T2, E&T3 are available on the Innovative Medicines website: http://europa.eu.int/comm/research/fp6/index_en.cfm?p=1_innomed

⁴⁹ CMC: Chemistry, Manufacturing and Control

⁵⁰ Wilson EO, *Consilience: The Unity of Knowledge*. ISBN: 0679450777

⁵¹ Busquin P, At the 'Communicating European Research' conference on 11 May 2004 http://ica.cordis.lu/search/index.cfm?fuseaction=news.simplifieddocument&N_RCN=22027&CFID=994044&CFTOKEN=61399528

tional medicine is 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 picture⁵².

- Scientists are urgently needed within these specific areas:
 - 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 (for example 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 specialist branches)⁵³ if they are to excel in modern risk assessment and risk management;
 - Pharmacology, non-clinical and clinical;
 - Postgraduate physicians specialised in pharmaceutical medicine;
 - Scientists skilled in bioinformatics, biosimulation, knowledge management, systems biology, systems toxicology, systems pharmacology and physiology (*in vivo* whole organism), pharmaceutical biotechnology, and *in silico* modelling;
 - Medical statisticians and biostatisticians;
 - Medical imaging is increasingly being used in both basic and clinical research. A need has been identified both in terms of trained scientists and technicians and in access to the technology, which is expensive to establish. This issue was dealt with in the efficacy part of this document;
- Establishing a curriculum for medicines development for professionals needing profound insight in the process;
- Continuous professional development, including an 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 fields such as veterinary medicine, pharmacy, biology, and medicine, where the focus is on the traditional career paths;⁵⁴
- The implementation of the Clinical Trial (GCP) directive⁵⁵ means there is a need for the 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 SMEs, especially in the early phases of medicines R&D, need an integrated overview of the medicines development process, including regulatory requirements, business skills and understanding of the business environment;
- Journalists, venture capitalists and the public lack an understanding of the conditions for and the process of medicines development, including the risk–benefit evaluation involved;
- 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.

⁵² Mankoff SP & al, Lost in Translation: Obstacles to Translational Medicine, Journal of Translational Medicine 2004, 2:14

⁵³ EUFEPS 2004, Report from EUFEPS Brainstorm Workshop on Safety Sciences, Brussels, April 2-3 • 2004

⁵⁴ However, some universities have included pharmaceutical medicine in the standard medical curriculum, e.g. University of Basel.

⁵⁵ 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 a strength and a weakness. The strength is the opportunity to view 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 academic research presence 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 the UK, Spain, Belgium, Sweden, Germany, France and Switzerland that are sought by professionals from outside Europe;⁵⁶
- Pharmaceutical and clinical sciences have a number of scientists who are highly visible on the international stage, and who act globally as leaders in the field;
- Europe has a good infrastructure to facilitate research, for example clinical trials;
- Cultural diversity provides an opportunity for viewing a challenge from a multitude of angles;
- Europe still has a strong biomedical industry presence.

European Weaknesses

- Shortage of funding for research;
- Insufficient co-ordination 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 the introduction of new molecular biological findings because of a 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 trans-national collaboration within E&T exist;⁵⁷
- Introduction of new technologies is slow;
- Recognition of the importance of trans-disciplinary research is limited;
- Intellectual property: it is much more difficult to obtain a European patent than 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;
- 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 for the benefit of science, patients and society.

⁵⁶ These courses are covered by a common syllabus co-ordinated by the International Federation of Associations of Pharmaceutical Physicians (IFAPP)

⁵⁷ ULLA: European University Consortium for Pharmaceutical Research, <http://www.u-l-l-a.org>

Threats

- The emerging economies in China and India could move high-level research and, thereby, education and training to their areas;
- Losing 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 vision and mission for the endeavour that follow 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 pan-European platform for education and training for professionals involved in biomedical R&D, including regulatory officers over the whole life-cycle of a medicine. The PhD programme supporting IMI activities has been completed.

The platform will include programmes for E&T covering the horizontal layer of integrated thinking over the entire medicines R&D process, as represented by the red oval in Figure 30 below, combined with specialised courses linked to the format for a registration dossier: non-clinical, quality and clinical, in the blue and yellow ovals in Figure 30. Furthermore, 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, such as journalists, venture capitalists and patients. By 2013, the suggested activities will have been implemented, and the results of this will be 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.

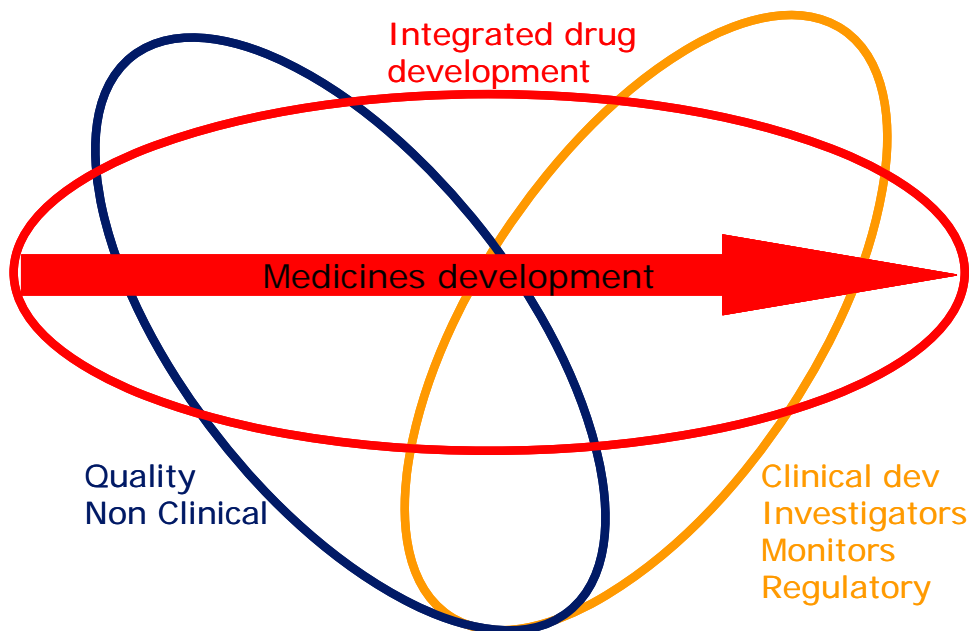


Figure 30 : Organisation of the E&T Platform.

The development of the E&T platform is in parallel with and supported by the Bologna Process, by which the European Higher Education Area⁵⁸ will be established in 2010 as a result of the 10 action lines from the Bologna process:⁵⁹

- Pan-European comparable degrees, based on a two-cycle system;
- An established ECTS⁶⁰ system of credits;
- Increased mobility of students and university staff;
- Established quality assurance standards for education;
- Implemented lifelong learning strategies;
- Active involvement of stakeholders in 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 postdoctoral⁶¹ education and training.

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 for 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 is to be achieved going forward:

- Establish a co-ordinating council, with the relevant stakeholders being represented,⁶² 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 the content of existing courses;
- Establish criteria for centres of excellence and, based on these, assessment of institutions already involved in E&T, and audit of E&T activities within disciplines;
- Identify centres and institutions with appropriate expertise to deliver courses and training;
- Overcome silo thinking. Pharmaceutical research is best done via a trans-disciplinary approach, but many researchers still think in disciplines in order to ‘protect’ their fields. This can be combated via:
 - Activities to make researchers realise that a combination of expertise improves research and innovation;
 - Stimulation of trans-disciplinary E&T, for example a 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;⁶³

⁵⁸ http://www.eua.be/eua/en/Research_linking.aspx

⁵⁹ <http://www.bologna-bergen2005.no/EN/BASIC/Pros-descr.HTM> and http://www.bologna-bergen2005.no/Docs/Norway/041014Fact_Sheet_Bologna-Process.pdf

⁶⁰ ECTS: European Credit Transfer System. http://europa.eu.int/comm/education/programmes/socrates/ects_en.html

⁶¹ Postdoctoral in this context means after obtaining a PhD or doctorate

⁶² 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

⁶³ 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

- Harmonisation of E&T on a European level to create a European Community of Pharmaceutical and Medicines Researchers. This requires pan-European grades to be established on the basis of the Bologna architecture, using the ECTS system;
- Develop regional Centres of Reference serving as clusters, and co-ordination of activities within a European sub-region;
- Ensure the qualification of enthusiastic and skilled scientists by encouraging the professional development of motivated individuals by embarking on MD and/or PhD programmes;
- Developing pharmaceutical medicine as a specific postgraduate discipline of medicine;
- Identify available finances to set up new courses and training facilities;
- Establish courses so stakeholders can easily obtain a basic knowledge of the whole R&D process, including an understanding of relevant regulatory guidelines;
- Provide training for people working in a scientific field who were not originally trained in that field. This covers both people changing their profile within a company (manager/project leader) or scientists who need knowledge within a new area of expertise. In addition, provide training to external stakeholders entering the field such as journalists;
- Constantly identify and update new scientific and technology developments and rapid implementation of corresponding training courses. Assess the current availability of expertise in new and emerging fields of technology across Europe, for example toxicogenomics and other omics, combinatorial chemistry, systems biology and nanobiotechnology;
- 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, including interaction with the Marie Curie units at the European Commission;
- Provide systematic postdoctoral E&T, and the necessary finance to support it. Generate a pan-European life-long learning initiative related to medicines research, including a credits system for professionals in the context of continued professional development (CPD), and update of original degree. This should be co-ordinated with other CPD programmes;
- Create standardised quality measures to be used for accreditation and evaluation of courses and guarantee sustainability. Expand the model across the different levels of education.

Management of European Medicines Research Academy (EMRA)

EMRA is a network of universities and higher education institutions. Further, EMRA is the co-ordinating body for activities related to Education and Training in the Innovative Medicines Initiative.

EMRA will be hosted by one of the participating universities as a central co-ordinating unit (the hub) at a location characterised by high-quality industry contacts and recognised science. The host university should have proven capabilities for international networking on E&T. The governance of EMRA will be handled by the EMRA Council, with representatives from:

- Participating universities and higher education institutions;
- Relevant learned societies;
- Industry;
- A few representatives from ministries responsible for higher education;
- Representative from the Bologna Process;
- Representatives from the IMI Safety, Efficacy and KM work streams.

The role of the EMRA Council is to follow the development of EMRA according to the plans that have been laid out, co-ordinate E&T activities in the IMI cornerstones of Safety, Efficacy, Knowledge Management and Education & Training, advice on E&T issues, and to provide recommendations to the IMI Scientific Committee on E&T.

5.5 Implementation Plan and Resources

The pan-European platform for education and training cannot be established overnight. Careful mapping of existing activities within E&T is needed, including the identification of European centres of excellence that can act as drivers and role models for other institutions and regions in Europe. Many proposals have been suggested during the consultation process with stakeholders. Based on the mapping, these proposals should be fleshed out with detailed implementation plans, including the evaluation of potential specific PhD grants. An E&T programme will be established to focus on scientific bottlenecks in the medicines R&D and management process, covering the following eight areas:

1. Integrated medicines development;
2. Ethics committee and patient organisation programmes;

3. Safety science programmes;
4. Other scientists within pharmaceutical R&D;
5. Pharmaceutical medicine professionals;
6. Regulatory affairs-based programmes;
7. Biostatisticians programme;
8. Bioinformaticians and biomedical informaticians programme.

The activities will be carried out with active participation of the relevant stakeholders, as shown below:

- The first priority is to establish a central co-ordinating unit;
- The second priority is to establish an advisory E&T council;
- Priority number three is to establish a programme for integrated medicines development and for ethics committees and patient organisations;
- The fourth priority is to establish programmes for safety sciences, and scientists within pharmaceutical R&D;
- Priority five is to establish programmes for pharmaceutical medicine professionals, regulatory affairs, biostatisticians, bioinformaticians and biomedical informaticians.

It is proposed that the third and fourth priority programmes are to be established at centres of excellence to be identified across Europe. Courses are to be held twice a year at four centres for each topic.

Within the first year, mapping to identify existing courses that will populate Figure 30 is a primary activity, as is planning the specific programmes set out below, together with a number of parallel activities. 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 gain an insight into the business-related aspects of R&D, it is recommended that 60 PhD grants should be established for each of the eight areas listed in the table below, i.e. 480 PhD grants. This programme should involve the co-operation of a university, a PhD fellow and an enterprise in a defined R&D project, linked to IMI activities, including PhDs covering the medicines development process. 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 the EC/Marie Curie Action programme, and 50% by the enterprise in question. To facilitate participation from SMEs, a proportion of these PhDs should be fully financed by the EC.

The plan is to roll out the PhD programme in three sequences. The first call will be in the second half of 2007, covering one-third of the programme, for commencement in 2008. The second and third calls will be in the second halves of 2008 and 2009, for commencement in 2009 and 2010. The PhD students will thus have completed their studies by 2013.

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

Activity	Duration (months)	Costs (€)
Short term budget		
Establish central co-ordinating unit, hiring personnel	3	20,000
Running central co-ordinating unit in the first year, including the following specific activities	12	355,000
Establish a council with representation of stakeholders	2	0

Activity	Duration (months)	Costs (€)
Meetings with the council, one every three months, 20 participants	12	90,800
1. Integrated medicines development, mapping and implementation plan (Priority score 10/10) Two meetings with relevant stakeholders (10 participants)	6	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	22,700
3. Safety science programmes, mapping and implementation plan (Priority score 9/10) Two meetings with relevant stakeholders (10 participants)	12	22,700
4. Scientists within pharmaceutical R&D, mapping and implementation plan (Priority score 9/10) Two meetings with relevant stakeholders (10 participants)	12	22,700
5. Pharmaceutical medicine, mapping and implementation plan (Priority score 9/10) Two meetings with relevant stakeholders (10 participants)	12	22,700
6. Regulatory affairs based programmes, mapping and implementation plan (Priority score 8/10) Two meetings with relevant stakeholders (10 participants)	12	22,700
7. Biostatisticians, mapping and implementation plan (Priority score 7/10) Two meetings with relevant stakeholders (10 participants)	12	22,700
8. Bioinformaticians and biomedical informaticians, mapping and implementation plan (Priority score 7/10) Two meetings with relevant stakeholders (10 participants)	12	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, identification of these centres Three meetings with relevant stakeholders (10 participants)	6	34,050
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	0
Revisit the evaluation process of academics, also considering industrial experience. Currently, 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	22,700
Open dialogue with EU member states on curricula	12	0

Activity	Duration (months)	Costs (€)
Establish European criteria for curricula. Although the ECTS system and the Bologna Process will result in broader comparability of degrees, for PhD courses in particular 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 ⁶⁴ Two meetings with relevant stakeholders (10 participants)	12	22,700
Explore an incentive system with EU-wide recognition and support to facilitate mobility of people to and from academia and industry Two meetings with relevant stakeholders (10 participants)	12	22,700
Establish an accreditation council for the European Medicines Research Academy Three meetings with relevant stakeholders (10 participants)	12	34,050
Map existing PPP in PhD training, e.g. graduate schools of research	12	0
Total short-term budget		783,650

The long-term budget to establish the E&T platform is pending mapping activities, as mentioned above, and detailed implementation plans. The following is, therefore, a rough estimate for a six-year period.

Activity	Costs (€mn)
Running central co-ordinating unit for six years	2.1
For each of the following programmes, the estimate is based on two courses per annum of one month duration for 26 participants in four centres of excellence across Europe	
1. Integrated Medicines Development	3.2
2. Ethics committee and patient organisation programmes	3.2
3. Safety science programmes	
3.1 Development of a new curriculum	0.5
3.2 Courses	3.2
4. Scientists within pharmaceutical R&D	3.2
5. Pharmaceutical medicine	3.2
6. Regulatory affairs based programmes	3.2
7. Bio-statisticians	3.2
8. Bioinformaticians and biomedical informaticians	3.2
480 PhD grants, 60 PhDs for each of the eight areas (€150,000 each)	72.0
Total long-term budget	100.2

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 those such as ethics committee members and representatives from patient organisations. Furthermore, the extent of co-financing via public-private partnership is not accounted for.

⁶⁴ The Zagreb Declaration 2004 on harmonisation of PhD programmes in Medicine and Health Sciences, http://bio.mef.hr/conference/docs/Zagreb_Declaration_UK.htm

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 attendees at courses, and qualifications achieved;
- Number of trainees employed in the 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 (this is a long term success measure);
- Raised level of innovation.

5.6 List of Contributors

Education & Training			
Stakeholders Group	Last Name	First Name	Institution
European Commission	Donnelly	Fergal	DG Research
	Hogan	Stephane	DG Research
	Norstedt	Irene	DG Research
	Schmitz	Bruno	DG Research
Academia	Algorta	Jaime	Foundation Leia
	Bjerrum	Ole J.	Danish University of Pharmaceutical Sciences
	Bryce	Charles	Napier University
	Bühler	Fritz	European Center of Pharmaceutical Medicine
	Catapano	Alberico L.	University of Milano
	Demotes-Mainard	Jacques	INSERM
	Duchêne	Dominique	Faculté de Pharmacie de Paris
	Ecker	Gerhard	University of Vienna
	Esquerra	Guifré	Generalitat de Catalunya
	Foth	Heidi	University of Halle
	Frokjaer	Sven	Danish University of Pharmaceutical Sciences
	Gennery	Brian	University of Surrey
	Godfraind	Théophile	Université Catholique de Louvain
	Holthoefer	Harry	Technomedicum, Finland
	Ja Crommelin	Daan	University of Utrecht
	Janko	Christa	Vienna School of Clinical Research
	Kaufmann	Jean-Michel	Université Libre de Bruxelles
	Martinez Arca	Sonia	Barcelona Scientific Park
	Meijer	Dirk K. F.	Groningen University
	Mosekilde	Erik	Danish Technical University
	Mulder	Gerard	Leiden University
	Noe	Chrisitan R.	University of Vienna
	Odysseos	Andreani D.	University of Cyprus
	Pellicciari	Roberto	University of Perugia
	Ronsisvalle	Giuseppe	University of Catania
	Rowland	Malcolm	University of Manchester
Sanz	Ferran	Universitat Pompeu Fabra	
Regulatory Authorities	Aronsson	Bo	EMA
	Purves	John	EMA
Companies, Pharma & SME	Benel	Laurent M.	Cephalon
	Boubekeur	Karima	Roche
	Collis	Michael G.	Pfizer
	Dirach (Chair)	Jorgen	NovoNordisk
	Farr	Ibrahim	Pivotal
	Fernandez-Cano	Paloma	MSD
	Fröstl	Wolfgang	Novartis
	Hughes-Wilson	Wills	EBE
	Lahuerta	Juan	GSK
	Lesur	Brigitte	Cephalon
	Lihanova	Zuzana	Biotika a.s.
	Michaelis	Uwe	MediGene AG
	Skingle	Malcolm	GSK
	Sterz	Helmut	Pfizer
	Strandgaard	Karen	EFPIA
	Van der Waart	Menno	Organon
	Wärngard	Lars	Vinnova
Patient Organisations	Poortman	Ysbrand	EPPOSI
Others	Crawley	Francis P.	Good Clinical Practice Alliance

6 Governance and Funding

This chapter presents the proposed governance structure of IMI, which has been prepared by the key IMI stakeholders: representatives of the European Commission, academia, biopharmaceutical companies and EFPIA. The recommendations on the IMI governance structure have also been reviewed by representatives from the Member States.

The following principles of governance are part of the proposal to grant Joint Technology Initiative (JTI) status to IMI, and will be implemented as soon as this status has been granted by the European Council.

6.1 Legal Status

The European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) will hold joint responsibility for creating and operating a JTI that will implement the recommendations of the IMI Strategic Research Agenda.

IMI will be established based on article 171 of the Treaty establishing the European Community ('The Community may set up joint undertakings or any other structure necessary for the efficient execution of Community research, technological development and demonstration programme'). The IMI legal entity will be an international not-for-profit organisation.

JTI status represents the highest level of pan-European public and private sector collaboration and co-ordination. This is needed because the scientific challenges addressed by IMI are too complex for organisations and/or nations to address in isolation. For IMI to succeed, it is essential that it is granted JTI status by the European Competitiveness Council after consultation of the European Parliament.

6.2 Structure

The IMI Joint Undertaking will have a legal mandate to award research grants to European Public–Private Collaborations. This organisation will have the responsibility of managing the involvement of stakeholders, as well as the operations required to support the implementation of the SRA. To fund, implement and operate IMI successfully, it is important that the structure of the IMI Joint Undertaking is flat and highly efficient. To support this objective, the organisational structure described in Figure 31 below is proposed for the IMI Joint Undertaking.

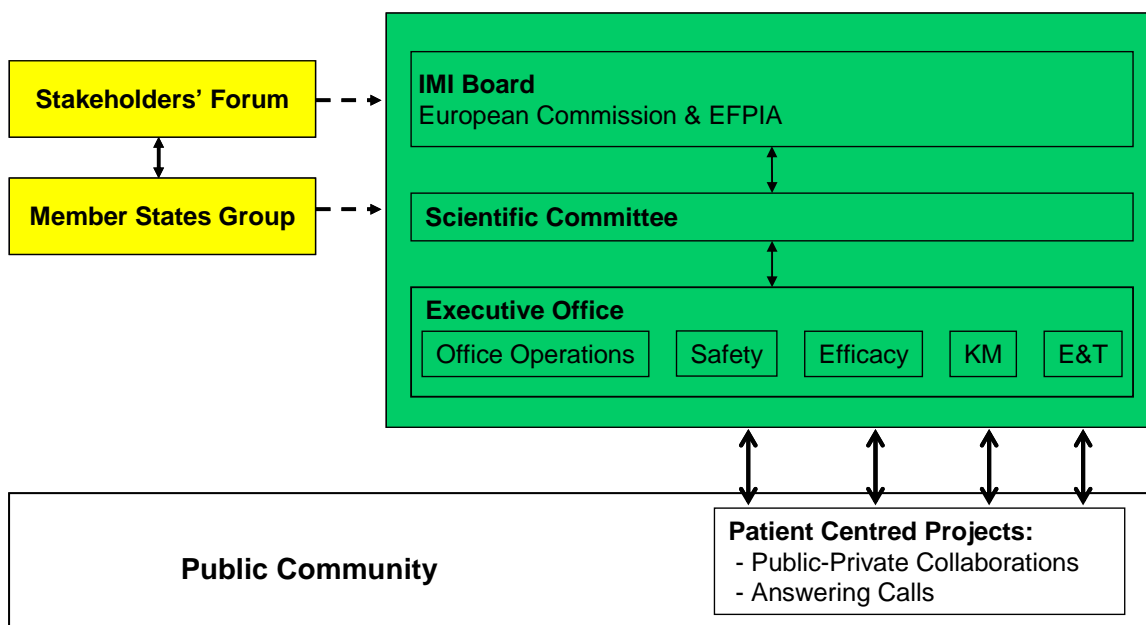


Figure 31 : Proposed IMI Implementation Structure

All stakeholders are eligible to participate in IMI projects, the only condition being that the research is performed in Europe. Therefore, there is no official membership of IMI.

The IMI organisation will comprise the following groups:

- The Member States Group, with nominees from all Member States and Associated Countries, will approve the composition of the Scientific Committee. It will facilitate rapid dissemination of information between IMI and Member State activities, and ensure co-ordination with Member State activities. In addition, it will play a leading role in the implementation of certain strategic parts of the SRA, such as Education & Training;
- The Stakeholders' Forum will be open to all stakeholders. It will convene annually at the General Assembly, where IMI activities will be presented and discussed to ensure openness and transparency to all stakeholders. In addition, the Stakeholders' Forum will be invited to provide advice to the Board on the orientation of IMI activities.
- The Board will be responsible for directing the operations of the IMI Joint Undertaking. The Board will oversee the implementation of the SRA by the Executive Office. Initially, the Board will be composed of representatives from the European Commission and EFPIA. However, based on future expressions of interest, new Board members representing other stakeholders may join;
- The Executive Office will be responsible for the overall operational and communication activities of IMI. It will develop a document termed 'Internal Regulation' which outlines the activities of the three IMI bodies, and how IMI will conduct its operations;
- The Scientific Committee will be an advisory body to the Board. It will conduct its activities in close liaison with, and with the support of, the Executive Office. It will consist of 15 members who reflect a balanced representation of both public and private stakeholders, including: academia, patients, industry and regulators. Collectively, its members will represent expertise from across the entire drug discovery and development process, and be expected to provide scientific recommendations on the scientific strategy of IMI.

Based on the recommendations presented in the SRA, the Executive Office will publish calls for research proposals that address the topics described in the SRA. Groups of partners (for example, academic institutions, SMEs, biopharmaceutical and healthcare companies, regulatory authorities and patients) will then form Public-Private Collaborations (PPCs) to propose research projects that address the topic of the respective call, and apply to IMI for funding. Each proposal will be prioritised and approved via a peer review process, on the basis of stringent scientific criteria and its potential impact on the IMI bottlenecks. The review and approval process will be developed by the Executive Office to ensure rapidity and transparency in the system. Academic institutions and SMEs within the PPC whose proposal has been approved will then receive funding from the IMI Joint Undertaking for the duration of the research project. As a guideline, a Public-Private Collaboration will consist of a minimum of one academic institution and/or one SME, plus one biopharmaceutical company which is a member of EFPIA.

Two contracts shall be signed to implement such a Public-Private Collaboration:

- The IMI Grant Agreement: the legal document that will govern the relationship between the partners and the IMI Joint Undertaking. The IMI Grant Agreement will be a high-level agreement that defines the specific project and the financing, as well as the application of the IMI Intellectual Property Policy;
- The Project Agreement: the legal document that will govern the relationship between the project partners, including detailed Intellectual Property Rights based on the IMI Intellectual Property Rights Policy (see Chapter 7). This system allows flexibility so that contractual obligations can be based on the project specifics, and so that the project agreement fairly reflects the scientific and commercial interests of all partners.

Micro, small and medium-sized enterprises or SMEs are defined by the European Commission as: enterprises which employ fewer than 250 persons and which have an annual turnover not exceeding €50 mn, and/or have an annual balance sheet total less than €43 mn⁶⁵. The IMI will apply the same definition.

⁶⁵ Article 2 of the Annex of the Recommendation 2003/361/EC

6.3 Funding

To implement fully the recommendations of the SRA will require about €460 mn per year for seven years starting in 2007 equally shared between FP7 and the EFPIA member companies.

FP7 will fund academic participants and support SMEs while biopharmaceutical companies will fund their own contributions to 100%. Other or non-biopharmaceutical companies participating in Public–Private Collaborations will be supported on a case-by-case basis. With this structure, public money will therefore go exclusively to public sector participants and SMEs, and not to biopharmaceutical companies. The biopharmaceutical industry partner(s) will provide R&D resources such as staff, laboratory facilities, materials and clinical research which will match the FP7 funds. The funding mechanism of IMI is described below in Figure 32.

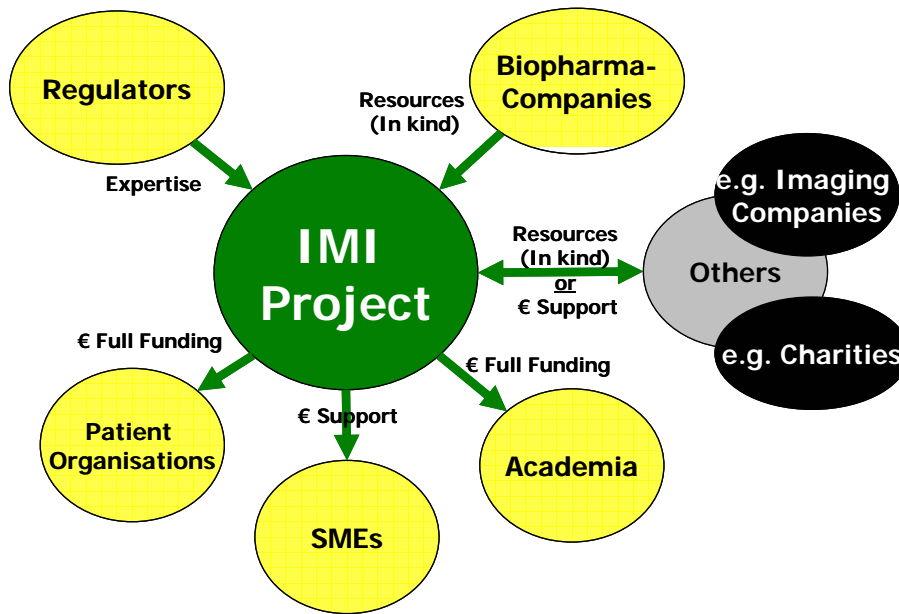


Figure 32 : IMI Funding Model

It is envisaged that the initial public funding could be about €50 mn (subject to yearly evaluation) and, therefore, the amounts shown below represent an estimated range of financial resources becoming available over the next seven years.

Source of funding	Recipient of funding	Estimated Costs Per Year (€mn)	
		2007	2013
European Union	Executive office	0.5	3
	IMI Project Participants: public institutions, patients organisations & SMEs	50	250
EFPIA	Executive office	0.5	3
Biopharmaceutical companies matching EU funds	IMI Projects Participants: biopharmaceutical companies	50	250

Figure 33 : IMI Funding Sources

Co-ordination of the IMI activities with the EU infrastructure funds is important, and therefore two representatives from IMI have been nominated for the committee responsible for the co-ordination of EU infrastructure funds in DG Research.

EU structural funds can also be used to establish R&D infrastructures; IMI will be in a unique situation to advice on how such infrastructures will best benefit the public–private biomedical community. To achieve this, IMI proposes to participate in committees responsible for the co-ordination of EU structural funds at the EU and/or national level.

6.4 Overview of IMI Costs by Pillar

The levels of investment required to support the recommendations related to each of the SRA Pillars have been estimated, and are summarised in Figure 34 below. These estimates are to be considered as preliminary estimates and subject to revision once the IMI is implemented. The duration of adopting the majority of the recommendations is between five and seven years, i.e. 2007–13.

Activities	Costs per year (€ mn)
Improve Predictivity of Safety Evaluation	165.4
European Centre of Drug Safety Research	36.7
Biomarker development	22.5
Relevance of rodent non-genotoxic carcinogenicity	22.5
Clinical safety and pharmacovigilance	68.7
IT infrastructure support	15.0
Improve Predictivity of Efficacy Evaluation	236.7
Cancer	66.7
Brain Disorders	62.3
Inflammatory Diseases	60.0
Diabetes	37.7
Infectious Diseases	10.0
Improved Knowledge Management for Better Decision Making	38.6
Running the KM Teams	3.3
KM Platform Infrastructure	8.4
KM Platform Research Projects	2.2
Translational KM Joint Projects	1.0
Translational KM Efficacy Support	23.7
Improve Education & Training to Develop the Talent Base	14.5
Create and run European Medicines Research Academy (3 FTEs)	0.4
Running of training programmes	3.8
PhD grants	10.3
Implementation: IMI Executive Office	6.0
GRAND TOTAL/YEAR	€0.46 bn
GRAND TOTAL IMI (2007–2013)	€3.23 bn

Figure 34 : Estimated Annual Costs of Implementation of the SRA

Figure 35 below shows that more than 50% of the proposed IMI budget is dedicated to improving the predictability of efficacy evaluation.

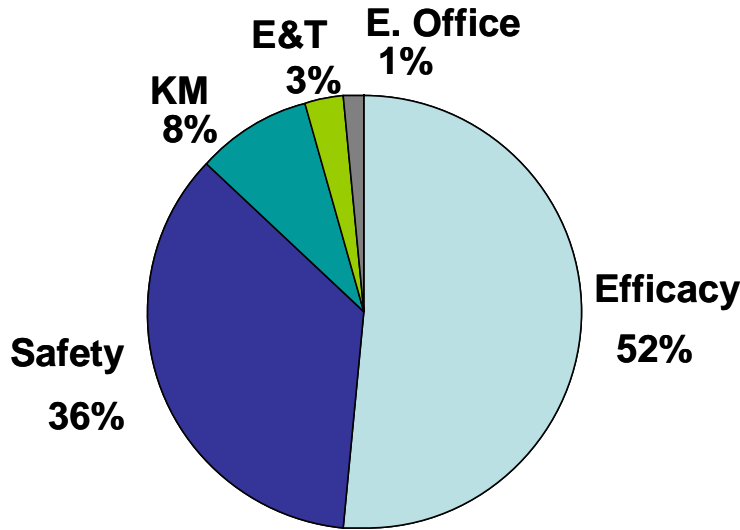


Figure 35 : Distribution of the SRA Total Yearly Costs (€0.46 bn)

6.5 Overview of IMI Costs by Type

General and Administration (G&A) costs are defined as general, administration and infrastructure costs. These include the costs of the Executive Office, of the overheads of the European Center of Drug Safety Research as well as the KM platform infrastructure and various co-ordinating activities such as communities of experts (CoEs). G&A costs represent a total of €33 mn per year or 7% of the total SRA budget the remaining being allocated to research projects. For comparison, InnoMed, the project of the 6th framework programme also have G&A costs of 7% of the total budget. IMI's total G&A costs of €33 mn per year are evenly distributed amongst the: Efficacy, Safety and KM Pillars of the SRA as described in Figure 36 below.

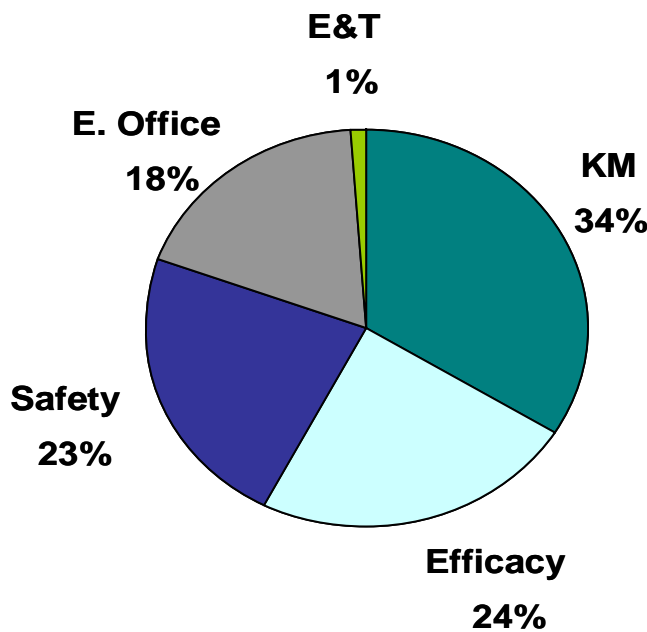


Figure 36 : SRA G&A Budget Cost Drivers

6.6 Communication

The future success of IMI depends on creating a high-performance collaborative culture, based on objective and transparent communications between all public and private stakeholders across Europe. To achieve this objective, effective communication is an important success factor for IMI.

To support this approach, the following communication tools and approaches will be implemented:

- IMI website with up-to-date information on the progress of the initiative;
- Annual General Assembly of the Stakeholders' Forum;
- Continuously updated material on IMI;
- Annual report;
- Introduction pack for the partners in Public–Private Collaborations;
- Press releases;
- Press conferences, when appropriate;
- The organisation of information days with Member States;
- Yearly status reports from Public–Private Collaborations;
- Final reports from Public–Private Collaborations to ensure a large dissemination of the results and of the potential application of these results to the biomedical R&D process;
- English as the official language to be used for all IMI communications.

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7 Intellectual Property

7.1 Objectives and Principles

The objective of the IMI intellectual property rights (IPR) policy is to promote knowledge creation and its exploitation as well as achieving broad participation in IMI projects of academic institutions, SMEs and biopharmaceutical companies.

This general IPR policy is designed to achieve broad participation in IMI, fair allocation of rights on generated IP in cases of commercial exploitation and to reward innovation. The proposed IPR Policy document is enclosed below and will be part of the IMI Internal Regulation document.

7.2 Intellectual Property Rights Policy

7.2.1 Definitions

“Background IPR” shall mean IPR owned by a Participant before the accession to the Grant Agreement and the Project Agreement, which are necessary and available for carrying out the Project or for using the Foreground IPR.

“Confidential Information” shall mean any and all written information exchanged between the Participants in the framework of the Project clearly identified or marked as being confidential at the moment of its disclosure, except for the information which the receiving party can prove (a) is, at the time of disclosure, in the public domain, (b) after disclosure, becomes part of the public domain by publication or otherwise, except by breach of this agreement by the receiving party, (c) is obtained from a third party not in breach of any obligation of confidentiality, (d) is known by the receiving party prior the date of the disclosure, (e) is required to be disclosed by the receiving party pursuant to any applicable law or judicial or governmental order, provided that the receiving party shall give immediate written notice of such requirement to the disclosing party with the view to agreeing the timing and the content of such disclosure. Any Confidential Information which is disclosed orally shall be confirmed in writing by the disclosing party within thirty (30) days after such disclosure.

“Direct Exploitation” shall mean the right to, or authorize others to, develop, sell, dispose, or otherwise commercialize products or processes which are the subject of the Foreground, Background or Side-ground IPR.

“Foreground IPR” shall mean IPR which is generated by a Participant in the performance of the Project other than Side-ground IPR.

“Grant Agreement” shall mean the agreement between the IMI Joint Undertaking and a representative of the Participants acting on behalf of the Participants. The Grant Agreements shall be negotiated and executed in accordance with this IPR Policy.

“Intellectual Property Rights” or “IPR” shall mean rights in data and information, inventions (whether or not patentable), patents and applications, know-how, copyrights, databases and designs.

“Participant” shall mean a legal entity (Legal Person) that participates in the Project as defined in the Grant Agreement. Contributions from third parties such as subcontractors do not constitute participation.

“Project” shall mean the research activity⁶⁶ carried out by the Participants under the IMI Joint Undertaking in accordance with the Grant Agreement .

“Project Agreement” shall mean the agreement between the Participants for the implementation of the Grant Agreement. The Project Agreements shall be negotiated and executed in accordance with the Grant Agreement and this IPR Policy.

“Project Objectives” shall mean the objectives which are defined in the Grant Agreement. The Project Objectives shall not include the direct development of marketable pharmaceutical or diagnostic products and the Grant Agreement shall not permit this.

⁶⁶ IMI Joint Undertaking will prepare model Grant Agreements. The Participants may use these model Grant Agreements as the basis of negotiation.

“Research Use” shall mean the right to, or authorise others to, make and use (but not sell or otherwise dispose of) products or processes which are protected by Foreground IPR or Background IPR necessary to use Foreground IPR for all purposes relating to research, discovery, development, approval and commercialisation of diagnostic or pharmaceutical products. Research Use includes research for commercial purposes by for-profit institutions and organisations.

“Side-ground IPR” shall mean IPR which are generated during the Project but which are incidental to the Project Objective as defined in the Grant Agreement and which is not needed to use Foreground IPR.

7.2.2 Ownership of IPR

7.2.2.1 Ownership of Background IPR

Each Participant will remain the exclusive owner of its Background IPR.

The Project Agreement shall identify the Background IPR and, where appropriate, identify any restrictions relating to the use and dissemination of such Background IPR. Each Participant shall disclose to other Participants prior to execution of the Project Agreement and to the Executive Office prior to execution of the Grant Agreement any such restrictions of which it is aware.

Each Participant shall remain free to license, assign or otherwise dispose of its ownership rights in Background IPR which is necessary for the use of Foreground IPR, subject to this IPR Policy and any rights and obligations of the Project Agreement.

7.2.2.2 Ownership of Foreground IPR

Ownership of the Foreground IPR belongs in the first instance to the Participant(s) who generated it. Each Participant shall ensure that Foreground IPR made, developed, or created by a third party acting on behalf of a Participant shall become the exclusive property of the Participant on whose behalf it was created. The Participants may agree on a different allocation of ownership in the Project Agreement.

Where several Participants have jointly carried out work generating Foreground IPR and where no individual Participant can be identified as its owner, such Participants shall, unless otherwise agreed in the Project Agreement, have joint ownership of such Foreground IPR. Unless otherwise agreed in the Project Agreement, and subject to any terms in the Project Agreement relating to such matters as fair compensation, each joint owner shall have the right to use and exploit such jointly owned Foreground IPR, including the right to grant non-exclusive licenses, without the consent of the other joint owners.

The ownership of, or rights in, Foreground IPR may be assigned or otherwise disposed of, as expressly permitted in the Grant Agreement and/or in the Project Agreement, or subject to the consent of all Participants, which may only be withheld where they can demonstrate that their rights would be adversely affected. Any such disposal shall be subject to this IPR Policy. Notwithstanding the above, a Participant may - without the permission of the other Participants - assign its Foreground IPR and/or its Background IPR to (i) its affiliates; or (ii) any purchaser of all or substantially all of its assets; or (iii) any successor entity resulting from the merger or consolidation of such party with or into such entities, provided that notice is served to all the other Participants and that assignee agrees in writing to be bound by the Grant Agreement, the Project Agreement and this IPR Policy.

7.2.2.3 Ownership of Side-Ground IPR

Ownership of the Side-Ground IPR belongs in the first instance to the Participant(s) who generated it. The Participants may agree on a different allocation of ownership in the Project Agreement.

7.2.3 Access Rights and License under Background IPR and Foreground IPR to the Participants for the purposes of completing the Project

1. The quality of the Foreground IPR and the capability to generate Foreground IPR relevant to the Project Objectives are essential considerations of the Grant Agreement.

2. During the performance of the project, each Participant undertakes to provide to the other Participants with the information that they reasonably need to perform their part of the Project and to undertake such joint effort as reasonably needed to achieve the Project Objectives. No Participant shall be obligated to give access to knowledge to a Participant unless such Participant can demonstrate that this knowledge is reasonably required by it to perform its part of the Project.

3. The Participants shall, unless prevented or restricted from doing so by obligations to others which exist at the date of accession to the Project Agreement, grant a royalty-free non-exclusive license under the Background and Foreground IPR to the other Participants solely for the purpose and to the extent necessary for undertaking and completing the Project unless local laws require otherwise and subject to appropriate undertakings of confidentiality.

4. The terms and conditions of access to information and of licenses as under 2 and 3 above shall be specified in the Project Agreement.

7.2.4 License under Background IPR and Foreground IPR after completion of the Project

7.2.4.1 Research Use By Participants

Each Participant shall disclose to other Participants prior to execution of the Project Agreement any restrictions of which it is aware and to the Executive Office prior to execution of the Grant Agreement which might prevent grant of licenses for Research Use as described below.

Foreground IPR shall be made available on a non-exclusive royalty-free basis to the other Participants, and their affiliates, for Research Use.

Background IPR necessary to use Foreground IPR for Research Use shall be made available on a non-exclusive basis to the other Participants, and their affiliates, to the extent reasonably required for the Research Use of Foreground IPR on fair and reasonable terms or royalty-free as determined in the Project Agreement.

7.2.4.2 Research Use By Third Parties

The Participants undertake to make available their Foreground IPR to third parties for Research Use on a non-exclusive basis under fair and reasonable terms, which may include free use. These terms shall be included in the Grant Agreement and shall be determined to encourage maximum Research Use for the intent stated in the Grant Agreement. In particular these terms and conditions will ensure that compensation for Research Use in regulatory submissions or to generate data intended for regulatory submissions is minimal.

The Participants shall also undertake to grant a non-exclusive license under fair and reasonable terms under their Background IPR, but only to the extent reasonably required for the Research Use of Foreground IPRs.

7.2.4.3 Direct Exploitation and other use of Foreground, Background and Sideground IPR

Participants may use, exploit, sublicense or otherwise commercialise their intellectual property rights as they see fit beyond the Research Use rights described in this IPR Policy. Where Direct Exploitation by a Participant or third party requires Foreground IPR or Background IPR necessary to use Foreground IPR owned by one of the Participants, its use will be negotiated between the parties involved as they see fit. Participants may agree such use rights in the Project Agreement.

7.2.5 Confidential Information

The Participants covenant not to disclose and not to use the Confidential Information received from other Participants except as provided in and for the purposes of the Project Agreement.

Unless otherwise agreed in Project Agreement, each Participant may publicly disclose (through journals, lectures, or otherwise) information relating to the results of the Project, provided that a copy of the proposed disclosure shall have been provided to the other Participants at least thirty (30) days prior to the submission of any written publication or any oral public disclosure to allow the Participants to determine whether any invention or Confidential Information would be disclosed. The reviewing Participants shall have the right to (a) require a delay in publication or presentation in order to protect patentable information, (b) require modifications to the publication for patent reasons or (c) require that Confidential Information be maintained as a trade secret.

7.2.6 Dissemination of Results

The Participants undertake to disseminate the results of the Project (as described in the Project Objective) as soon as reasonably practicable but not later than one (1) year after the termination or expiry of the Project. The Project Agreement shall include a description of the material which must be published in accordance with the IPR Policy.

If the Participants do not publish within such time periods without good reason, the Executive Office has the right to disseminate such results in a manner consistent with the Grant Agreement.

7.3 List of Contributors

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8 Appendices

8.1 Consolidated List of Contributors in Alphabetical Order

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	Weir	Neil	UCB
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	Wells	Tim	Serono
	Westwick	John	Novartis
	Williams	Pauline	GSK
Patient Organisations	Baird	Jesme	Cancer Patient Coalition
	Dedes	Nikos	European AIDS Treatment Group
	Georges	Jean	Alzheimer Europe
	Henrichs	Helmut	International Diabetes Federation
	Johnstone	Robert	People with Arthritis/Rheumatism in Europe
	Kent	Alastair	Genetic Interest Group
	Le Cam	Yann	EURORDIS European Org. for Rare Disorders
	Newton	Alistair	EFNA
	Oosterwijk	Cor	EGAN
	Poortman	Ysbrand	EPPOSI
	Schöffski	Patrick	European Cancer Patient Coalition

Stakeholders Group	Last Name	First Name	Institution
Patient Organisations	Van Der Streichel	Didier	European Cancer League
Others	Brendel	Carole	EURADIA
	Bundule	Maija	Latvia Ministry of Education and Science
	Capart	Gilles	ProTon Europe
	Crawley	Francis P.	Good Clinical Practice Alliance
	Dar	Ora	Ministry of Industry and Trade, Israel
	Dawson	Bill	EUFEPS
	De Groot	Mark	LAREB
	Eibe Guijarro	Carmen	Zelita
	Hall	Charlotte	Swedish Ministry of Education
	Hartgerink	Jan Willem	Ministerie van Volksgezondheid
	Helgesen	Gro	Research Council of Norway
	Holsapple	Michael	ILSI/HESI
	Hurtenbach	Ursula	Deutsches Zentrum für Luft und Raumfahrt e.V. Projektträger für das BMBF Gesundheitsforschung
	Lindén	Hans H.	EUFEPS Secretariat
	Maspous	Bosch	Ramon
	Montuenga	Luis	CIMA
	Moquin-Pathey	Carole	ESF
	Nagl	Bernadette	Consultora Projectes Europeus
	Peracino	Andrea	Lorenzini Foundation
	Sazhenova	Nataly	Socium' Foundation
Sormann	Monika	"Ministry of Flanders Technology and Innovation Division"	
Steininger	Birgit	FFG Austrian Research Promotion Agency	
Van Dongen	Martinus	InnoTact Consulting B.V.	
Vericat	Joan Albert	IVTIP	
Wijnberg	Bart	Ministerie Van Volksgezondheid	

8.1.2 Barcelona Meeting 2005 Participants

Stakeholders Group	Last Name	First Name	Institution
European Commission	Donnelly	Fergal	DG Research
	Dusinska	Mária	DG Research
	Heynisch	Thomas	DG Enterprise
	Hogan	Stéphane	DG Research
	Lucaroni	Beatrice	DG Research
	Norstedt	Irene	DG Research
	Quintana	Octavi	DG Research
	Rainer	Bernd	DG Research
Academia	Alonso	Fernandez Maria José	University of Santiago de Compostela
	Artursson	Per	University of Uppsala
	Bermejo	Marival	University of Valencia
	Bjerrum	Ole J	Danish Univ. of Pharmaceutical Sciences
	Boissel	Jean-Pierre	Service de Pharmacologie Clinique
	Buckle	Derek	Royal Society of Chemistry
	Buonocore	Giuseppe	European Society for Paediatric Research
	Caldwell	John	University of Liverpool
	Camí	Jordi	Institut Municipal d'Investigació Mèdica
	Carné	Xavier	Hospital Clinic Sant Cugat

Stakeholders Group	Last Name	First Name	Institution
Academia	Catapano	Alberico L	University of Milan
	Crommelin	Daan JA	Utrecht University
	Demotes-Mainard	Jacques	Hôpital Cardiologique, CIC INSERM
	Duchêne	Dominique	Faculté de Pharmacie de Paris Sud J.B.
	Ecker	Gerhard	University of Vienna
	Eldem	Türkan	Hacettepe University
	Foth	Heidi	University of Halle
	Gennery	Brian	University of Surrey
	Kauffmann	Jean-Michel	University Université Libre De Bruxelles
	Lanciego	Jose L	Neuromorphology-Tracing Lab
	Loza	García María Isabel	University of Santiago de Compostela
	Matyus	Peter	Semmelweis University
	Meijer	Dirk K F	Groningen University
	Mosekilde	Erik	Danish Technical University
	Mota-Filipe	Helder	University of Lisbon
	Mulder	Gerard J	LACDR, Leiden University
	Mutuberria	Ricardo	University Pompeu Fabra
	Negruta	Mircea	Medica Romania
	Noe	Christian R.	Vienna University
	Odysseos	Andreani D	University of Cyprus
	Pelkonen	Olavi R	Univeristy of Oulu
	Pellicciari	Roberto	University of Perugia
	Pitris	Constantinos	University of Cyprus
	Plasencia	Carmen	Centre de Recerca i Investigació de Catalunya
	Postaire	Eric	INSERM DAPS
	Prous	Blancafort Josep	Prous Institute for Biomedical Research
	Ronsisvalle	Giuseppe	University of Catania
	Rowland	Malcolm	University of Manchester
	Sanz	Ferran	University Pompeu Fabra
	Silva Lima	Beatriz	Instituto Nacional de Farmácia
	Tamargo	Juan	Universidad Complutense
	Timmerman	Henk	Vrije Universiteit (Free University)
	Tsantili-Kakoulidou	Anna	University of Athens
Vladimirov	Iavor	Sofia Center of Reproductive Medicines and IVF	
Vuorela	Pia	University of Helsinki	
York	Peter	Institute of Pharmaceutical Innovation	
Regulatory Authorities	Bass	Rolf	Office for Medicinal Products
	Hoefnagel	Désirée	Ministry of Health, Welfare and Sport
	Le Courtois	Patrick	EMA, European Medicines Agency
	Graffner	Christina	Medical Products Agency
	Purves	John	EMA
	Torrent-Farnell	Josep	EMA
Companies	Åkerlund	Anders	AstraZeneca
	Alonso	Villanueva Sara	BIONOSTRA S.L.
	Barilero	Iman	Johnson & Johnson
	Benel	Laurent M	Cephalon
	Boubekeur	Karima F.	Roche
	Casari	Georg	ORIDIS Biomed
	Cuervo	Virginia	PharmaMar S. A.
	de la Viña	Gloria	New Biotechnic S.A.
	Dirach	Jørgen	Novo Nordisk A/S

Stakeholders Group	Last Name	First Name	Institution
Companies	Farr	Ibrahim	Pivotal S.L.
	Farrelly	Adeline	EuropaBio
	Fernández	Cano Palom	Merck Sharp & Dohme
	Foley	Paul M	BiInnovationsZentrum
	From	Per	Astra-Zeneca
	Fröstl	Wolfgang	Novartis Pharma AG
	Grandjean	Nicolas	Novartis Pharma AG
	Hague	Jeremy	Xceleron Ltd
	Haluza	Radovan	Generi Biotech s.r.o.
	Holthöfer	Harry	Director of Technomedicum
	Kettling	Ulrich	DIREVO Biotech AG
	Knowles	Jonathan F.	Roche
	Kuniaková	Renata	Pleuran s.r.o.
	Lahuerta	Juan	GSK
	Lappin	Graham	Xceleron Ltd
	Leblanc	Bernard	Pfizer
	Lesur	Brigitte	CRDC Cephalon France
	Lihanova	Zuzana	Biotika a.s.
	Marchand	Benoit	NovaXon BV
	Mescheder	Axel	MediGeneAG
	Nebout	Thierry I.R.I.S.	Servier
	Párraga	Antonio	Esteve
	Pfannkuch	Friedlieb F.	Roche
	Prats	Cot Carles	Esteve
	Ragan	C. Ian	Elli Lilly
	Seiler	Jürg P	ToxConSeil
	Simon	Laureano	Progenika Biopharma S.A.
	Söhngen	Mariola	PAION Deutschland GmbH
	Stegemann	Sven	Pfizer
	Sterz	Helmuth	Pfizer
	Strandgaard	Karen	EFPIA
	Taboryski	Rafael	Sophion Bioscience
	Ursing	Björn	Medivir
Urzay	J	Farmaindustria van Dongen Martinus BM Inno-Tact Consulting B.V.	
Vankova	Nina	Meditrial	
Vasquez	Tatay	Enrique Neocodex	
Vela	Carmen	Ingenasa	
Vendrell	Montse	Barcelona Scientific Park	
Veromaa	Timo	Biotie Therapies Corp.	
Von Ahsen	Uwe	Biovertis-Information Driven Drug Design	
Wärngård	Lars	Vinnova	
Patient Organisations	Kent	Alastair	Genetic Interest Group
	Le Cam	Yann	EURORDIS European Org. for Rare Disorders
Others	Algorta	Jaime	Fund. LEIA
	Crawley	Francis	EFGCP Secretariat
	Eibe Guijarro	Carmen	Zelita
	Esquerrà	Guifré	Generalitat de Catalunya
	Lindén	Hans H.	EUFEPS Secretariat
	Martinez	Arca Sonia	Barcelona Scientific Park
	Maspous	Bosch	Ramon
Montuenga	Luis	CIMA	

Stakeholders Group	Last Name	First Name	Institution
Others	Moquin-Pathey	Carole	European Science Foundation
	Nagl	Bernadette	Consultora Projectes Europeus
	Sazhenova	Nataly	Socium' Foundation
	Steininger	Birgit	FFG Austrian Research Promotion Agency
	Terrón	Fernández	Fernando Medina Terrón & Asociados
	Van Dongen	Martinus	InnoTact Consulting B.V.

8.2 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

8.3 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
<p>1. Lawrence RC <i>et al.</i> (1998), Felson DT <i>et al.</i> (1987 and 1995) Lanes SF <i>et al.</i> (1997), Bolen J <i>et al.</i> (2002). 2. Yoshida S <i>et al.</i> (2002) 3. Hochberg <i>et al.</i> (1995) and RCGP 1991 Morbidity stats from General Practice and applied to US data. 4. Carmona L <i>et al.</i> (2001) 5. Felson <i>et al.</i> (1998) Stakeholder Insight: Osteoarthritis Survey (Q1.5) used to extrapolate total OA prevalence from studies on a single joint.</p>			

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
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
Main 5 EU male	9.0	121.3	171.0	123.7	424.9
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
<i>* UN database figures</i>								
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 100,000	inci-per	Annual incidence	inci-
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 <i>et al.</i> , Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. <i>Gastroenterology</i> . 1998 Jun; 114 (6): 1161-1168. Erratum in: Loftus EV Jr, Reply. <i>Gastroenterology</i> . 1999 Jun; 116 (6): 1507.					
Japan: Morita N <i>et al.</i> , Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. <i>Journal of Gastroenterology</i> . 1995 Nov; 30 Suppl 8: 1-4.					
France: prevalence: German prevalence applied to French population; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Germany: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Italy: prevalence: Trallori G <i>et al.</i> , A population-based study of inflammatory bowel disease in Florence over 15 years (1978-92). <i>Scandinavian Journal of Gastroenterology</i> . 1996 Sep; 31 (9): 892-899; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Spain: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
UK: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 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, 1000s	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 <i>et al.</i> , Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. <i>Gut</i> . 2000 Mar; 46 (3): 336-343.					
Japan: Morita N <i>et al.</i> , Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. <i>Journal of Gastroenterology</i> . 1995 Nov; 30 Suppl 8: 1-4.					
France: prevalence: German prevalence applied to French population; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Germany: prevalence: Dirks E <i>et al.</i> , [Prospective study of the incidence and prevalence of ulcerative colitis in a large urban population in Germany (western Ruhr area)]. <i>Zeitschrift für Gastroenterologie</i> . 1994 Jun; 32 (6): 332-337; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Italy: prevalence: Trallori G <i>et al.</i> , A population-based study of inflammatory bowel disease in Florence over 15 years (1978-92). <i>Scandinavian Journal of Gastroenterology</i> . 1996 Sep; 31 (9): 892-899; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Spain: prevalence: Saro Gismera C <i>et al.</i> , [Incidence and prevalence of inflammatory bowel disease. Asturian study in 5 areas (EIICEA). Spain]. <i>Anales de Medicina Interna</i> . 2003 Jan; 20 (1): 3-9; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
UK: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , 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). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					

8.4 Inflammatory Diseases Detailed Analysis

8.4.1 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 is 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 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.	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.
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		

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.	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 Bio-Imaging 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		

8.4.2 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.	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		
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	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

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.	Develop biochemical marker kits for in office physician use.	Important for early disease detection, prognostication and early therapy.								
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	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			

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.	Safety biomarker for immunosuppressive side-effects. This is a necessity in RA where physicians are uneasy with broad immunosuppressives.	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				
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				

8.4.3 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	
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

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 excellence, 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
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	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	

8.4.4 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.

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 excellence, 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
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	
Develop better disease models (especially in-vivo), which are more predictive for drug efficacy.	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.	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.

8.4.5 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.	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)

8.5 Glossary

Associated State	Five states which are party to an international agreement with the European Union under the terms or on the basis of which it makes a financial contribution to all or a part of the Framework Programme: Iceland, Israel, Liechtenstein, Norway and Switzerland
Bottlenecks	The principal causes of delay in the biomedical R&D process
Candidate Country	Candidate Countries are the four states acknowledged by the European Union as candidates for accession to the European Union: Bulgaria, Croatia, Romania and Turkey
European Technology Platform (ETP)	<p>The European Technology Platforms concept is an initiative led by the European Commission aimed at increasing the competitiveness of Europe as an area for industrial R&D investment within the context of the Lisbon Objectives.</p> <p>With industry in the lead, ETPs unite stakeholders around a common vision and approach for the research needed, focussing particularly on the definition of a Strategic Research Agenda (SRA) and the mobilisation of critical mass for the research and innovation effort.</p> <p>The IMI is an ETP to be implemented as a JTI.</p>
Executive Office	One of the bodies of the IMI Joint Undertaking responsible for overall operational and communication activities of IMI Joint Undertaking. The Executive Office will develop a document termed Internal Regulation, which explains the activities of the IMI bodies and how IMI will conduct its operations.
Four-Pillars	<p>Four areas in the biomedical R&D process where bottlenecks occur on which the SRA recommendations were based:</p> <ol style="list-style-type: none"> 1. Predictivity of Safety Evaluation (Pillar I) 2. Predictivity of Efficacy Evaluation (Pillar II) 3. Knowledge Management (Pillar III) 4. Education and Training (Pillar IV).
IMI Board	<p>One of the bodies of the IMI Joint Undertaking. It is responsible for directing the operations of the IMI Joint Undertaking and overseeing the implementation of the SRA by the Executive Office.</p> <p>The initial Board will contain members of the European Commission and EFPIA</p>
IMI Grant Agreement	Contract, which governs the relationship between the Project Partners and the IMI Joint Undertaking. The IMI Grant Agreement shall be a high-level agreement that defines the specific project, the financing and the application of the IMI Intellectual Property Policy.
IMI Joint Undertaking	The Joint Technology Initiative focusing on the implementation of the IMI Strategic Research Agenda.
InnoMed	Integrated Project (IP) funded through the third call of the 6 th Framework Programme of the European Commission. InnoMed addresses two topics: predictive toxicology and biomarkers in Alzheimer's Disease. It represents a pilot project for IMI.

Innovative Medicines Initiative (IMI)	<p>A unique pan-European public and private sector collaboration between large and small biopharmaceutical and healthcare companies, regulators, academia and patients.</p> <p>The aim of the Innovative Medicines Initiative is to support the faster discovery and development of better medicines for patients and enhance Europe's competitiveness by boosting its research-based biopharmaceutical sector.</p>
Joint Technology Initiative (JTI)	<p>Joint Technology Initiatives (JTI) is a new public-private partnership concept proposed by the European Commission for the 7th Framework Programme where the scale and complexity of research needs require significantly increased research efforts, both public and private. JTI status represents the highest level of pan-European public and private sector collaboration.</p>
Micro, Small and Medium Sized Enterprises (SMEs)	<p>Enterprises which employ fewer than 250 persons and which have an annual turnover not exceeding € 50 mn, and/or have an annual balance sheet total less than €43 mn.</p>
Project Agreement	<p>Contract, which governs the relationship between the project partners, including detailed Intellectual Property Rights.</p>
Project Partners	<p>The organisations participating in a Public-Private Collaboration.</p>
Public-Private Collaboration (PPC)	<p>A group of stakeholder organisations of the Innovative Medicines Initiative conducting a Research Project.</p> <p>As a guideline, a Public-Private Collaboration shall consist of at a minimum – one academic institution and/or one SME plus one biopharmaceutical company (member of the EFPIA).</p>
Research Directors Group (RDG)	<p>The Research Directors Group of EFPIA contains representatives from 25 biopharmaceutical companies with European R&D operations.</p>
Scientific Committee	<p>One of the bodies of the IMI Joint Undertaking. The Scientific Committee will be an advisory body to the Board. It will conduct its activities in close liaison and with the support of the Executive Office. It shall consist of 15 members who reflect a balanced representation of both public and private stakeholders (e.g. academia, patients, industry and regulators). Collectively, its members will represent expertise across the entire drug discovery and development process and be expected to provide scientific recommendations on the scientific strategy of IMI.</p>
Seventh Framework Programme (FP7)	<p>The 7th Framework Programme is a set of the actions at the European Union level to fund (approximately of €54 bn) and promote research for the period 2007 to 2013. It is one of the main initiatives linked to the Lisbon agenda for European growth and competitiveness.</p>
Sixth Framework Programme (FP6)	<p>The 6th Framework Programme is the European Union's main instrument for research funding. It has a budget of €17.5 bn over four years from 2002 to 2006.</p>
Strategic Research Agenda (SRA)	<p>The SRA describes recommendations to address the bottlenecks in the biomedical R&D process and proposes a plan to guide their implementation.</p>

8.6 Abbreviations Used

AD	Alzheimer's Disease
ADRs	Adverse Drug Reactions
BLA	Biological License Application
Bn	Billion
BSE	Business Enterprise Sector
BSTP	British Society of Toxicological Pathology
BTS	British Toxicology Society
CAGR	Compound Annual Growth Rate
CHMP	The Committee for Medicinal Products for Human Use
CoEs	Communities of Experts
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
DB	Database
E	Estimate
EBE	European Biopharmaceutical Enterprises
EC	European Commission
ECDSR	European Centre of Drug Safety Research
ECTP	European Centre of Toxicologic Pathology
EFB	European Federation of Biotechnology
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMRA	European Medicines Research Academy
EORTC	European Organisation for the Research and Treatment of Cancer
EPF	European Patients Forum
ESTP	European Society of Toxicological Pathology
ETP	European Technology Platform
ETS	European Toxicology Society
EU-25	The 25 Member States of the European Union
EUFEPS	European Federation for Pharmaceutical Sciences
FP	Framework Programme
GBAORD	Government Budget Appropriations or Outlays on R&D are all appropriations allocated to R&D in central government or federal budgets.
GDP	Gross Domestic Product

GLP	Good Laboratory Practices
HCP(s)	Health Care Professional(s)
HESI	Health and Environmental Sciences Institute
IBD	Inflammatory Bowel Disease
ILSI	International Life Sciences Institute
IMI	Innovative Medicines Initiative
IP	Integrated Project
IPRs	Intellectual Property Rights
IT	Information Technology
JTI	Joint Technology Initiative
KM	Knowledge Management
LEEM	Les entreprises du médicament
mn	Million
NCE	New Chemical Entity
NIH	National Institutes of Health (US)
NME	New Molecular Entity
OA	Osteoarthritis
POM	Proof-of-Mechanism
PPPs	Public–Private Partnerships
QOL	Quality of Life
R&D	Research and Development
RDG	Research Directors Group
SME	Small and Medium-Sized Enterprises
SRA	Strategic Research Agenda
STRPC	Science Technology Regulatory Policy Committee