



## **Innovative Medicines for Europe**

Abbreviation: InnoMed

Vision:

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

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## Executive Summary

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The discovery and development of new drugs is very costly and attrition rates are high. Initiatives to reduce the rate of attrition during later phases of development are clearly desirable and if successfully implemented will reduce costs. The InnoMed strategy addresses the complex issues associated with the future of biomedical research in the EU, and addresses ways of achieving accelerated development of, safe and more effective medicines, aiming to revitalize the European biopharmaceutical research environment.

InnoMed's wide consortium base, being led by the European Federation of Pharmaceutical Industry and Associations (EFPIA), guarantee's a commitment from all the stakeholders needed to change the process of drug development in Europe.

The course for addressing the necessary changes is to first develop a Strategic Research Agenda (SRA) that will encompass the whole path from discovery of a new drug target to the validation and approval stages of a new drug compound. This will be agreed by all the relevant stakeholders via meetings and workshops. Four key bottlenecks in the drug development process will be addressed:

- Safety
- Efficacy
- Knowledge Management
- Training and Education

This comprehensive strategy with a detailed roadmap will lead to the deployment of a European Technology Platform (ETP). This European Technology Platform will deliver added value to the drug discovery and development process and to individual stakeholders by providing a more effective healthcare, vibrant and dynamic scientific environment and will create a significant economic value through small and large enterprises in Europe. Therefore the industry is firmly committed to the development and implementation of the Strategic Research Agenda.

## Introduction

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Europe has lost its major place as a global centre for biomedical research. Despite a five-fold increase in the Pharmaceutical trade surplus over the last 5 years, investment in R&D is declining markedly in comparison with the US. Over the last decade the US has invested far more in public sector sponsored biomedical research, Europe has not yet matched this level of public sector investment. This is affecting, and will continue to affect, growth and development in Europe to the detriment of both patients and society.

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

The discovery and development of new drugs is very costly and the rate of failure of drug candidates is high. Initiatives to reduce the rate of attrition during later phases are clearly desirable and if successfully implemented will reduce development costs. Then Europe can again become a place where Industry chooses to invest. EFPIA's Research Directors Group has identified pre-competitive barriers to innovation, around which industry and stakeholders in the drug development process can collaborate to achieve this goal. The barriers on which this proposal is focused are the failure of preclinical studies to predict safety and efficacy in the clinic and the regulatory process, which has not kept pace with scientific developments. Improvements in predictive biology and the incorporation of these new concepts into an improved regulatory framework would decrease the cost of drug development and speed the delivery of innovative medicines to patients.

## European Technology Platform

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A European Technology Platform is an instrument under development by the European Commission to address major economic, technological or societal challenges enabled by Research and Development. It is intended as a means to foster effective public-private partnerships between all relevant stakeholders, in effect to implement Strategic Research Agendas across Europe. It is anticipated to contribute to achieving the Lisbon objectives, developing the European Research Area and increasing investment in R&D towards the 3% of GDP target. This intention was published in the Communication from the Commission entitled "Science and technology, the key to Europe's future – Guidelines for future European Union policy to support research"<sup>1</sup>.

Based on this the European Commission asked EFPIA's Research Directors Group (RDG) to identify main barriers to innovation in Life Sciences research in Europe with the objective of establishing a European Technology Platform for Innovative Medicines. The RDG has already identified main pre-competitive barriers to innovation, around which industry and stakeholders in the drug development process can collaborate to achieve a first class environment for R&D. This project is intended to further develop the Strategic Research Agenda together with mobilising stakeholders into a consortium that can implement this agenda via a European Technology Platform.

In this context there are many possibilities and opportunities that will help Europe towards more efficient drug development, examples include:

- Leverage expertise in new technologies for identification and validation of biomarkers
- Manage and organise data to create knowledge to predict benefit and risk of new therapies to the benefit of all stakeholders in the drug development process
- Improve dialogue with regulators during development prior to regulatory approval to help reduce requests for additional data and regulatory questions following submission
- Build and support pre-competitive research centres and a European network of centres of excellence

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<sup>1</sup> COM(2004) 353 final

Initiatives such as these must be funded, coordinated and targeted to have the maximum impact, and this is where the creation of a European Technology Platform (ETP) to manage the initiatives is both important and relevant.

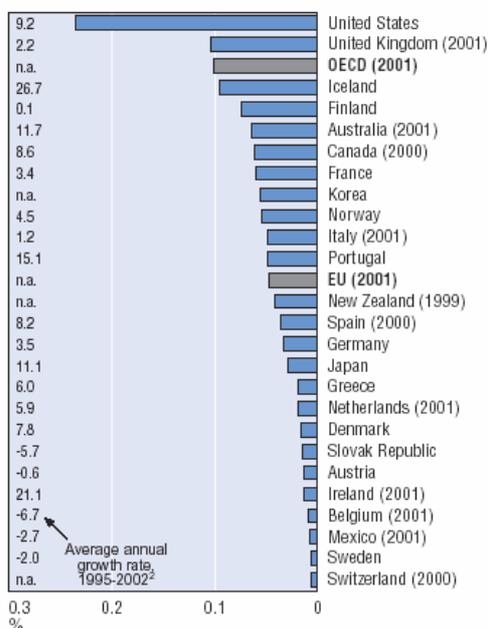
To be effective, the European Technology Platform must deliver added value to the drug discovery and development process and to individual stakeholders. The collective benefit is expected to come from a transparent, total-systems approach to the discovery and development process. This enables each player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

## Relevance to the objectives of the EU Life Sciences Priority

The LifeSciHealth thematic priority aims to stimulate and sustain multidisciplinary basic research to exploit the full potential of the human genome information to underpin applications to human health.

The InnoMed project addresses this by its focus on integrating genomics information in the drug discovery and development process. Advances in molecular genetics and molecular biology offer the possibility of identifying novel drugable targets that could be modulated in order to prevent, control, or even cure, many of the diseases of which we currently have only a limited understanding in terms of their pathophysiology and aetiology. Furthermore, advances in pharmacogenetics could make a dramatic contribution to improving treatment of patients by identifying those populations whose genetic profile determines how they may, or may not, respond to a specific drug treatment. Thus, advances in the technology of genetic screening might help to predict favourable drug responses, leading to "tailored medicine".

Between 1998 and 2003, the US government doubled the funding for the National Institutes for health. Direct health R&D funding actually fell in the late 1990s in a number of countries.

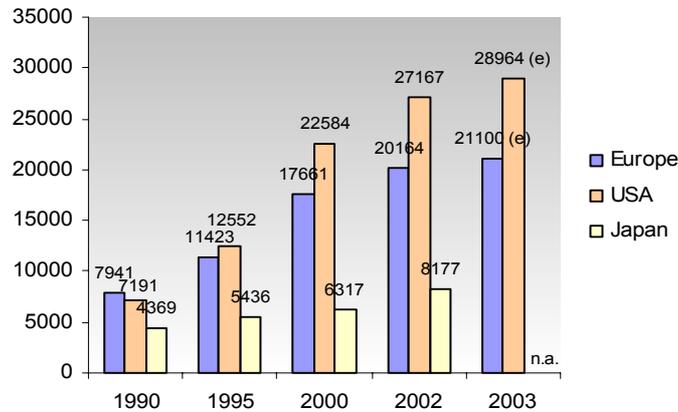


**Figure 1. Health R&D in government budgets as a percentage of GDP, 2002<sup>2</sup>**

Over the past ten years, Europe’s research and development basis has gradually eroded, with new leading-edge technology research units being transferred out of Europe, mainly to the United States. Whereas R&D investments in Europe grew by 2.6 times between 1990 and 2003, the corresponding increase in the U.S. is more than fourfold. In 1990, major European research-based companies spent

<sup>2</sup> OECD, R&D database, June 2003

73% of their worldwide R&D expenditure on the EU territory. In 1999, they spent only 59% on the EU territory. The USA was the main beneficiary of this transfer of R&D Expenditure.



**Figure 2. Pharmaceutical R&D expenditure in Europe, USA and Japan 1990-2003<sup>3</sup>**

European Technology Platforms or technology initiatives are one of six major objectives for future EU Research proposed by the Commission in a recent communication<sup>4</sup>. **"Technology Platforms"** bring together companies, research institutions, the financial world and the regulatory authorities at the European level to **define a common research agenda** which should mobilise a critical mass of - national and European - public and private resources.

The creation of the ETP through InnoMed will ensure that the EC goals for a common research agenda has been achieved as the SRA proposed in InnoMed will be driven by the stakeholders, and InnoMed will ensure that a critical mass has been mobilised to implement the ETP. This should contribute to reverse the relative decline in pharmaceutical R&D expenditure in Europe as it will once again be in the interests of all stakeholders to work within an innovative European biopharmaceutical research environment.

## Potential impact

On January 23, 2002, the Commission published its Communication on Life Sciences and Biotechnology – a Strategy for Europe<sup>5</sup>. Life sciences and biotechnology are widely regarded as one of the most promising frontier science and technology areas for the coming decades. Life sciences and biotechnology entail and foster the development of many enabling technologies – like information and nano-technologies – and cover a wide range of applications with benefits in both the public and private sectors. On the basis of scientific and technological breakthroughs in recent years, the explosion of genomic data on living organisms is posed to spur much new research and applications in the future according to this report.

The High Level Group on innovation and provision of medicines, which brought together different stakeholders (European commission, government representatives, industry, patients and healthcare providers) agreed on the following recommendations relating to the research and development environment (Recommendations 8 and 9 of the G10 report ‘Stimulating Innovation and Improving the EU Science Base’<sup>6</sup>).

<sup>3</sup> EFPIA member associations, PhRMA, JPMA, Data 2003: estimate EFPIA & PhRMA (Mio euros (at 2002 exchange rates))

<sup>4</sup> COM(2004)353 "Science and technology, the key to Europe's future - Guidelines for future European Union policy to support research"

<sup>5</sup> [http://europa.eu.int/comm/biotechnology/pdf/com2002-27\\_en.pdf](http://europa.eu.int/comm/biotechnology/pdf/com2002-27_en.pdf)

<sup>6</sup> <http://pharmacos.eudra.org/F3/g10/g10home.htm>

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

To support the Lisbon objective, a communication from the Commission from June 2004<sup>7</sup>, acknowledged the need to double the Union's research budget and emphasised the launch of European technology initiatives. In the same paper, the need for a European level co-ordination of research efforts and for the development of research infrastructures are presented as key factors to stimulate research in Europe.

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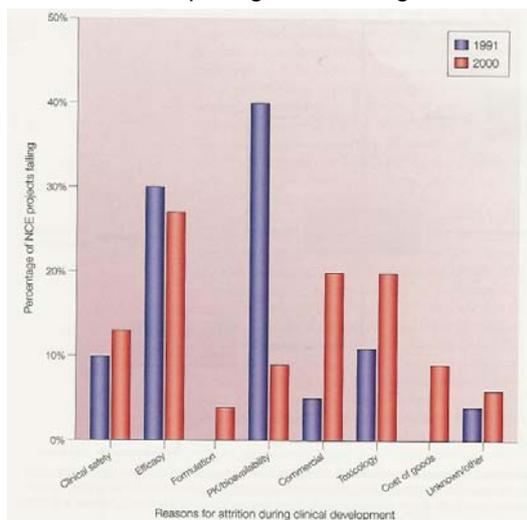
<sup>7</sup> Science and technology, the key to Europe's future – Guidelines for future European Union policy to support research

# Strategic Research Agenda

In order to implement a European Technology Platform InnoMed will first need to build a comprehensive strategy with a detailed roadmap that will lead to the ETP. This will be a proposed Strategic Research Agenda (SRA) that will encompass the whole path from discovery of a new drug target to the validation and approval stages of a new drug compound. The SRA will address key areas, which are linked to the bottlenecks in current drug development and will also include regulatory aspects.

## Bottlenecks in the R&D Process

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



**Figure 3. Reasons for attrition <sup>10</sup>**

The commonest factors resulting in project failure are either lack of efficacy (25%), clinical safety concerns (12%) and toxicological findings in pre-clinical evaluation (20%). The biggest advance has been in improving the predictive value of studies of drug metabolism in optimising drug design. This has been possible because in-vitro screens of absorption and metabolism have been validated by subsequent correlation with clinical measurements. A Technology Platform, as proposed by InnoMed, with an academic, industry multi-disciplinary collaboration aims to achieve similar clinical correlations within the other areas mentioned in the figure above. These improvements can be related to the different stages of drug discovery and development.

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

<sup>9</sup> Industry Success Rates 2004, Centre for Medicines Research International Ltd. CMR04-234R, May 2004

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

The objective for the future would be to identify as soon as possible:

- A lack of efficacy, despite promising pre-clinical data
- The potential for adverse drug reactions and pre-clinical toxicity

The identified key bottlenecks in the R&D process are shown in the figure below. In these areas, scientific and technological advances, as would be gained with the ETP would be of direct benefit to the pharmaceutical industry by improving efficiency and containing costs. In addition, a more efficient R&D process will bring more efficacious and safer drugs to the market, resulting in a direct benefit for the patients. InnoMed addresses issues in all of these areas, and within a European Technology Platform all of these topics will help improve the overall efficiency of medicine development.

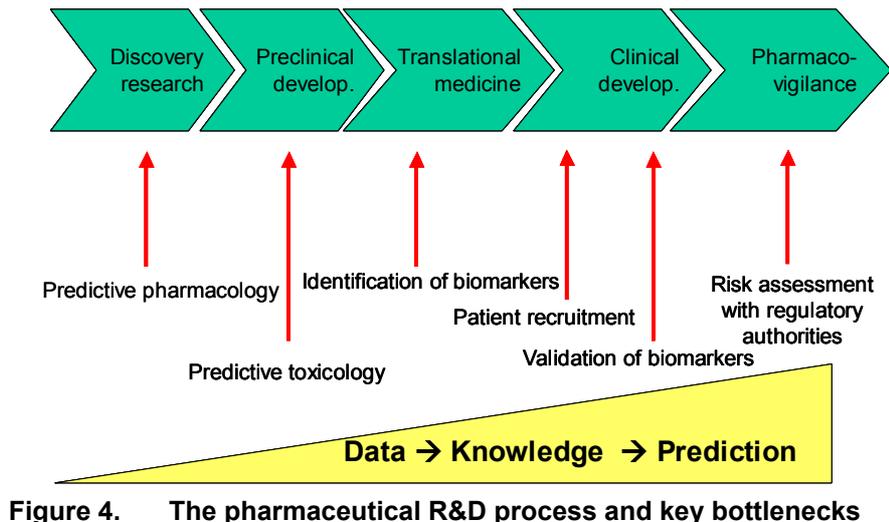


Figure 4. The pharmaceutical R&D process and key bottlenecks

## Cornerstones of the Strategic Research Agenda

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

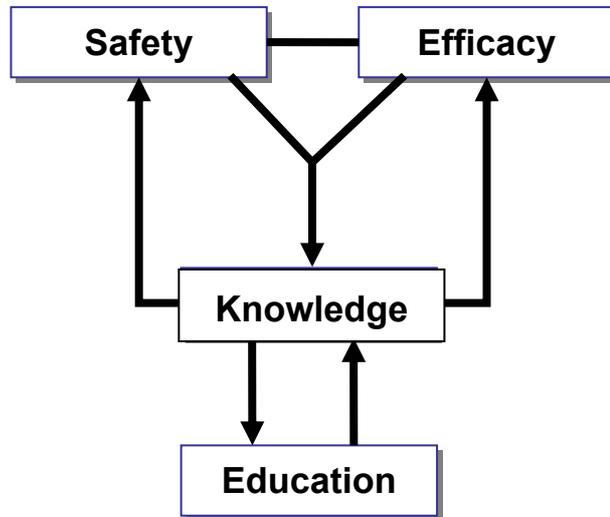
- Safety, addressing the bottlenecks predictive toxicology and risk assessment with authority
- Efficacy, addressing the bottlenecks predictive pharmacology, biomarkers identification and validation, patient recruitment and risk assessment with authority
- Knowledge Management, leveraging the potential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

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

The long term benefits to this approach will be to:

- Accelerate development timelines and therefore reduce development costs
- Discover and develop better medicines, which will be safer, have a better efficacy and will be better adapted to patients needs
- Facilitate risk / benefit evaluation by the authorities to accelerate access of innovative medicine to the patients

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



**Figure 5. Strategic Research Agenda interactions**

# Safety

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## Introduction

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Regulatory authorities are becoming more risk-averse - translating into increasing risk management planning which can include requirements for expanded studies to quantify potential serious adverse events. The reasons for this may include increased public and media scrutiny of pharmaceuticals and regulatory decision-making and a perceived lack of robustness of the post-marketing monitoring processes. In addition, there is an increasing tendency for approval of more restricted indications (with requests for increased data for broader indications); this can lead to significant delays in gaining marketing authorisation and delay patient access to innovative medicines that address medical needs. The following suggestions are intended to enhance this overall process.

The SRA will address this:

- By establishing processes to improve the predictability of toxicology experiments using integration of new technologies such as toxicogenomics, toxicoproteomics and toxicometabonomics
- By involving the regulatory authorities in the development of these new processes so that the data can support the risk/benefit evaluation process

## Action Plan

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Over 30% of compounds in development in 2000 failed because of toxicities in animals not detected early in the development programme or unexpected adverse events in clinical studies<sup>11</sup>. There have been significant advances in four areas of technology relating to the detection of possible hazards. These technologies include:

- In silico tools to aid the detection and prediction of toxicities
- Toxicogenomics, i.e. detecting drug induced changes in gene expression in cells (determined by mRNA measurements)
- Toxicoproteomics, which is the detection of abnormal patterns of proteins
- Metabonomics which is the detection of changes in endogenous cellular metabolism of a cell or organism

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

The main purpose of funding research in these new technologies is to evaluate their utility in preclinical safety testing. Once established the challenge will be sharing the application of these technologies in preclinical safety testing and training and educating scientists from industry and in the Regulatory Authorities in their use and value. There is a need to identify how much expertise and experience in the use of these technologies is currently available within Europe and to share this information between the different stakeholders.

The ultimate goals must be to:

- Assess the use and value of integrating results from 'omics technologies together with the results from more conventional toxicology methods in more informed decision making in preclinical safety testing

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<sup>11</sup> Nature Rev. Drug Discov. 3, 711-715, 2004

- Initiate and support the development of scientists within the novel field of Systems Toxicology
- Initiate steps to get acceptance by Regulatory Authorities of the value of this approach

These challenging goals are reachable by an international collaborative approach. InnoMed will establish a network of scientists who will:

- Collect information on prior knowledge (already available expertise, experience and methodology)
- Consult with potential academic and biotech partners on the best approaches to reach the desired goals
- Define the agenda for future studies based on inputs received from the different companies and additional inputs developed in collaboration with all stakeholders

To achieve these goals, at least, the following stakeholders will be involved:

- European-based, research-intensive pharmaceutical companies which have already considerable knowledge in the field of classical toxicology and 'predictive' toxicology
- SME companies with expertise in the disciplines needed (e.g. software-developer, data-base provider; chip producers and other technology manufacturers)
- European University Laboratories with focused expertise
- European and American Regulatory Agencies
- The initiative from the Health Environmental Sciences Institute on nonclinical/clinical safety correlation
- The Safety working group from the InnoMed consortium member EUFEPS
- The Toxicogenomics working group from the InnoMed consortium member EFPIA

# Efficacy

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## Introduction

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There are two strategic requirements if the availability of improved medicines for society has to be enhanced. These are an improved early safety evaluation and secondly an improvement in clinical research including translational medicine.

Within InnoMed an improvement in clinical research with regards to efficacy and patient recruitment will be addressed with the following actions:

- Improve prediction of efficacy using biomarkers
- Develop strategies towards medicines which will be better adapted to patients' needs
- Improve patients' recruitment using biomarkers and consultation of patients and clinical groups
- Increase the dialogue with regulatory authorities in order to shorten or reduce the cost of clinical development

## Action Plan

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The objective is to improve the process of bringing new medicines to market and to reduce development costs. Recommendations will be developed for increasing the predictability of efficacy testing focusing on three key areas, biomarkers, patient recruitment and regulatory approvals.

### *Biomarkers*

To improve prediction of efficacy, recent scientific advances have suggested the use of biological markers (biomarkers). Biomarkers are 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'<sup>12</sup>.

Biomarkers can provide new insights into a drug's mechanism of action, metabolism, efficacy and/or safety and into disease mechanisms and disease course. They can play multiple roles during the research and development phase of a drug. Biomarkers can be used as a tool to understand the biology of a disease but also to understand the effects of a new drug. Biomarkers may also provide information on patient sub-populations that might respond to a new drug or be susceptible to side effects. This approach is known as patient stratification.

The value of biomarkers is that they hold enormous potential to point us in the direction of critical information for developing better diagnostics and drugs, helping the industry to manage the innovation process in a more cost-effective manner. Specifically, biomarkers can generate value by:

- Facilitating more cost-efficient drug development through better and faster decision-making in research. Biomarkers may provide information that helps make go or no-go decisions sooner, enables to zero in on safety and efficacy issues faster, and guides in designing better and more cost-effective clinical trials
- Directing the development of marketable diagnostic applications
- Select the right drug for the right patient in terms of efficacy and safety

These result in more targeted, clinically differentiated medicines that can be marketed more effectively because of their superior benefits. Doctors can prescribe them with greater confidence, patients can take

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<sup>12</sup> Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," Clinical Pharm. & Therapeutics, vol. 69, N. 3, March 2001

them with better response and fewer side effects, and the healthcare system can utilize them with better healthcare outcomes and greater overall cost-effectiveness.

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 valid 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'.

This strategic objective aims at leveraging academic and clinical expertise to identify biomarkers using innovative technologies such as 'omics technologies and imaging. Groups with specific disease expertise need to be set up to review the existence of biomarkers and to define strategies to find new biomarkers and to validate them.

#### *Patient Recruitment*

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

Strategies will be developed with clinicians and patient associations on how to improve patient recruitment. A potential approach could be through education of patients about the benefits of participating in research. Patients should be informed to a certain extent about the outcome of the clinical research. In this respect some initiatives proved to be useful, e.g. participation of patient organizations in study groups to reflect upon trial strategy for therapeutic and diagnostic innovations and participation of patients at various stages of the clinical trials elaboration process. A systematic analysis of patient's participation needs to be performed with the relevant European medical research and patient associations.

#### *Regulatory Approvals*

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

1. Improve dialogue with regulators during development prior to regulatory approval to help to reduce requests for additional data and regulatory questions following submission
2. 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)
3. Increase the involvement of other stakeholders such as patients in the regulatory review process. Patients often take a different view of the risks that they are prepared to take when weighed up with the potential benefits of a new medicine

4. Develop the methods to collect data on risks and benefits of medicines once they are available in a real-world setting. Evaluation of the long term and real life benefits and risks of medicines after launch should use information from randomised clinical trials and from observational/epidemiological studies where required that use electronic patient-level data (e.g. data from medical records). It is therefore important that databases containing this information are developed and these resources made available for academic and industry research
5. Develop and ensure adequate use of early conditioned approval for innovative new medicines with an adequate safety profile

To achieve these goals, at least, the following stakeholders will be involved:

- European-based, research-intensive pharmaceutical companies
- SME companies such as members of EBE and EuropaBio
- Medical research associations such as the European Medical Research Council (EMRC)
- Academics associations, including the InnoMed consortium member, the European Federation for Pharmaceutical Sciences (EUFEPS)
- Regulatory agencies e.g. EMEA and national agencies
- Patients associations such as the European Patients Forum (EPF)

# Knowledge Management

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## Introduction

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The advancement of science (e.g. high-throughput technology, pharmacogenomics, pharmacogenetics, translational medicine) allows the generation of an enormous amount of data. Data is essential for the successful transition of candidate molecules to effective medicines; however, the challenge is to turn data into actionable knowledge through adequate integration. Bioinformatics and Medical Informatics are disciplines that up to now have followed separate development with few contacts and synergies between them in Europe. Biomedical Informatics is the emerging discipline that aims to join these two worlds together so that the discovery and creation of novel diagnostic and therapeutic methods is fostered<sup>13</sup>.

In principle, there are two levels of knowledge management that need to be addressed:

- The capture, analysis and interpretation of knowledge generated regarding the physiology and pathophysiology related to disease stage or toxicological targets. Here the aim is to improve the understanding of the underlying process including the impact of pharmacogenomics in order to predict successfully the validity of a drug target and risk management for patient populations
- The capture, analysis and interpretation of knowledge generated for one potential drug candidate from discovery, non-clinical and clinical development all the way to lifecycle management. The aim here is to integrate all available knowledge at any given stage of the development process in order to make the best predictions possible for the chances of success of this molecule in the next stage

## Action Plan

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The goal of this work is to improve the way data is managed and to create knowledge to predict the benefits and risks of new therapies.

Within InnoMed this will be addressed with the following actions:

- Develop a strategy to identify the areas of interest to all stakeholders and to create a collaborative framework for companies and academic groups
- Provide the framework to allow the collection of data in a collaborative manner, enabling synergies and avoiding duplication of effort
- Develop a strategy to build powerful computer models to capture and integrate information related to disease stages and related to molecules

### *Knowledge Management for Diseases and Adverse Side Effects*

The emerging field of System Biology is aimed at capturing the increasing knowledge in physiology, pathophysiology etc. However, it is not enough to just compile list of pathways, enzyme reactions, transporters etc, it is also important to link the individual elements by appropriate computer models in order to be able to understand how the system would react to a specific challenge. These types of models are principally possible (e.g. Diabetes model by Entelos), however, they are complex and can only be established through collaboration of scientists across different disciplines.

- Areas of common interest need to be identified and all information that is relevant for the system needs to be captured and shared. These areas could be diseases such as Diabetes or Inflammatory diseases, but they could also be toxicological targets such as the liver or the heart. A special area would also be metabolism and drug-drug interactions, where the understanding of

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<sup>13</sup> Sanz et al Current perspective of information technologies in drug discovery. J. Comput Aided mol Des 2002; 16:767-8

common pathways and the regulating system is essential for the prediction of the behaviour of concomitant medications

- Alliances with academia need to be established in order to get the state-of-the-art scientific input. A good example for a European initiative is the Drug-Drug interaction prediction software SimCYP, which is developed by the University of Sheffield in collaboration with a Consortium of Pharmaceutical Companies (e.g. Pfizer Europe, Novartis, Novo Nordisk, Servier)
- Powerful computer models need to be built in order to capture and integrate the information that can then be accessed to simulate possible scenarios. Special attention needs to be paid to include the biological variability into the models in order to reflect the entire patient population and not just the “average patient”

#### *Knowledge Management for Drug Candidates*

Powerful database structures need to be established in order to allow easy integration of all relevant information regarding one drug candidate such as in vitro data, pre-clinical pharmacology, drug metabolism and pharmacokinetics (DMPK), toxicology, human pharmacokinetics, human efficacy and safety as well as drug-drug interactions.

This data needs to be combined by computer models that link the pharmacokinetics of the compound with efficacy and safety also taking into account influence factors such as pharmacogenomics, concomitant medication, disease state etc. The model would be started with the first available knowledge and then continuously updated as information becomes available. At every important drug development decision point (e.g. first dose to man, dose selection for Phase 2, transition into Phase 3) the model would be used to predict the potential outcome of the next Phase. With increasing integrated information, the uncertainty of the predictions becomes smaller.

The know-how for an integrated model-based Drug Development tool is available in Europe. There are a number of Universities such as Manchester (UK), Leiden (NL) and Uppsala (SE) that have been active contributors in advancing the science in this field. The major bottlenecks in this field are:

- Lack of availability of databases across R&D that allow easy access for data integration
- The currently available software is outdated. For software providers this is not an attractive field as the number of users is limited. A European working group with representatives from Novartis, GSK, Novo Nordisk, Servier, Pfizer and Roche has been formed to explore possibilities to drive this forward
- The number of trained experts in this field is still limited and industry funded training programs will be needed to meet future needs for respective scientists

For the Strategic Research Agenda existing Knowledge Management initiatives in Europe will be identified. Together with the relevant stakeholders these will be evaluated, and gaps to address the issues will be identified along with solutions. The SRA will:

- Develop a strategy to identify the areas of interest to all stakeholders and to create a collaborative framework for companies and academic groups
- Develop a strategy to build powerful computer models to capture and integrate information related to disease stages and related to molecules

To achieve these goals, at least, the following stakeholders will be involved:

- European-based, research-intensive pharmaceutical companies
- SME companies developing software such as Entelos
- Academic groups specialised in data management and bioinformatics such as the Research Unit on Biomedical Informatics (IMIM-UPF)
- Academic groups specialised in system biology such as Prof Hengartner (ETH)

# Education and Training

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## Introduction

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

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

- The current organisation of universities facilitates building of “silos” where each scientific area has its own life without much interaction with other areas. This is contributing to the fragmentation of European research<sup>14,15</sup>
- There are weak or non-existing links between basic scientists and clinical scientists. This gap is critical and is yet not bridged. Efforts are done in the field of translational medicine to bridge this gap from “bench to bedside” – and back again by combining a thorough understanding of the biology of a disease with the clinical picture<sup>16</sup>
- There is a need for safety scientists with a much broader spectrum of knowledge than the traditional toxicologist. The future safety scientist will have to integrate knowledge accumulated from many safety-relevant disciplines (primary and secondary pharmacology, functional genomics, safety pharmacology, physiology, pathophysiology physical chemistry, animal and clinical toxicology cellular biology; biochemistry and animal physiology with all their special branches) to excel in modern risk assessment and risk management<sup>17</sup>
- In most European countries the scientific interaction between scientists in academia, industry and regulatory authorities are minimal and often the movement of intellect is uni-directional towards the industry. However, scientist from academia and regulatory agencies need to be involved and have access to new technologies
- European education needs to strive for excellence and competitive systems need to be put in place for a continuous improvement of the scientific level in Europe

To identify ways to overcome these gaps consultation with the involved stakeholders is needed in order to propose how to reorganise education & training and to design specific training programmes

## Action Plan

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The use of many new technologies calls for greater integration of the activities and a more holistic view to ensure a cohesive medicines development process. To achieve this it is necessary to ensure that education and training is targeted and that the new breeds of scientists are aware of the needs of these new technologies.

Within InnoMed this will be addressed with the following actions:

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<sup>14</sup> Wilson EO, Consilience : The Unity of Knowledge. ISBN: 0679450777

<sup>15</sup> Busquin P, At the 'Communicating European Research' conference on 11 May 2004  
[http://ica.cordis.lu/search/index.cfm?fuseaction=news.simpledocument&N\\_RCN=22027&CFID=994044&CFTOKEN=61399528](http://ica.cordis.lu/search/index.cfm?fuseaction=news.simpledocument&N_RCN=22027&CFID=994044&CFTOKEN=61399528)

<sup>16</sup> Mankoff SP & al, Lost in Translation: Obstacles to Translational Medicine, Journal of Translational Medicine 2004, 2:14

<sup>17</sup> EUFEPS 2004, Report from EUFEPS Brainstorm Workshop on Safety Sciences, Brussels, April 2-3 • 2004

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

The participating stakeholders, in particular EFB Section on Medicines Development and EUFEPS, but also the Universities involved in the project and other partners, are deeply integrated within the international bio-pharmaceutical research community and important training programmes exist. Most partners are members of Editorial Boards of Pharmaceutical Science, Biotechnology and Bioinformatics journals, such as the European Biotechnology News, New Drugs, IEEE Transactions in Neural Networks and others. Also, most of them are active in their national Pharmaceutical or Biotechnology Associations. InnoMed will exploit this network of scientific relationships to increase the resonance of project.

### **Consultation with stakeholders on the gaps identified in education and training**

A briefing document based on the gaps identified will be issued and sent to relevant stakeholders to expand this gap analysis and to address the issues mentioned above.

Stakeholders to be heard will include industry organisations (EFPIA, EBE), academic organisations (EFB Task Group on Education and Mobility, EUFEPS Committee on Training and Education), Clinicians (Faculty of Pharmaceutical Physicians and others), Patient organisations, regulatory bodies. This document will be then further refined and finally adopted by all stakeholders concerned in the process.

A workshop will be organised to gather the relevant stakeholders to provide qualified input. The workshop will discuss the following issues:

- Expansion of the gap analysis within education and training to ensure alignment with the strategic Research Agenda
- Creation of a pan-European platform for research, research training and technology development supporting the entire medicines development and approval process. This will address the G10 recommendation 8 on creation of the European virtual institutes of health, connecting all existing competence centres on fundamental and clinical research into a European network of excellence. It will further address the issue on fragmentation of European research and the outflow of excellent European scientists to other parts of the world. The scope could be to establish a European Medicines Research Academy (EMRA). The basis could be one major research and training facility in an EU member country, possibly established as an extension of a current university or hospital site. A number of centres of excellence or other relevant partners will be associated with EMRA in order to ensure a network that covers all relevant competencies in the field of medicines development and approval. The goal is to create a centre with the following ambitious goals:
  - Training: The quality of research and training at EMRA should attract the best Ph.D. students from all over Europe
  - Research: The research environment at EMRA should be so attractive that the best scientists and other expertise from all over the world would consider spending time at EMRA
  - Mobility: Within the participating centres of excellence, mobility of both researchers and students should be encouraged both within EMRA and between academia and industry
- The need for training courses in medicines development for people from academia, research institutions and SMEs
- Development of a curriculum for the safety scientist

The Consortium will identify the relevant institutions to be invited to the workshop. Institutions will include Universities, research institutions, regulatory agencies (EMA).

**Exchange training programme**

The exchange training programme would contribute to the spreading of excellence and the integration of European research efforts. The programme will include:

- Exchange training visits for doctoral students affiliated with the consortium. These visits will be aimed at the acquisition of new skills, in particular the analysis of large data sets with updated analytical packages and the best statistical tools for the management of knowledge generated in this IP
- Exchange training visits for postdoctoral fellows and research staff within the consortium. Postdoctoral staff and research staff will be offered a possibility to visit another institution for 1 to 6 months. The objectives of these visits will include the formulation of standards for joint research, planning and design of joint projects and the preparation of reports

# Stakeholders

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

Stakeholders	Benefits
<b>Patients and patient organisations</b>	<ul style="list-style-type: none"> <li>• Improved quality of life through improved/more appropriate therapies</li> <li>• Improved quality of life through increased national GDP/capita</li> <li>• Influence on the research agenda for new medicines</li> </ul>
<b>Clinicians</b>	<ul style="list-style-type: none"> <li>• A mechanism for influencing the development of more appropriate therapies and adding to their armoury of treatment options</li> <li>• Better diagnostic tools and methods</li> </ul>
<b>Governments</b>	
Treasuries	<ul style="list-style-type: none"> <li>• Increased GDP/capita through the increased international competitiveness and growth of the European based bio-pharmaceutical industry</li> <li>• Reduced cost of working days lost to disease</li> <li>• Positioning Europe as the leader in pharmaceutical and biopharmaceutical R&amp;D, raising its international profile, attracting international partnerships and inward investment</li> <li>• Creation of jobs / reverse movement of high skill jobs from Europe</li> <li>• Providing a forum for increased commercialisation of pharmaceutical research</li> </ul>
Health Departments	<ul style="list-style-type: none"> <li>• Improved integration of the development of therapies for unmet medical needs</li> <li>• More effective therapies will mean more efficient treatment and reduced costs for long term care</li> </ul>
<b>European Institutions</b>	<ul style="list-style-type: none"> <li>• Contribution to the Lisbon agenda</li> </ul>
<b>Regulatory agencies</b>	<ul style="list-style-type: none"> <li>• Development of new risk/benefit assessment methods in collaboration with all relevant stakeholders</li> </ul>
<b>Industry</b>	
Big Pharma	<ul style="list-style-type: none"> <li>• Reduced risk and a more productive drug pipeline</li> </ul>
Biotechnology companies	<ul style="list-style-type: none"> <li>• An improved environment for discovery and early</li> </ul>

Stakeholders	Benefits
	stage development of enabling technologies, diagnostics and potential therapies
Insurance industry	<ul style="list-style-type: none"> <li>• Reduced liabilities for long term care</li> </ul>
Other economic sectors	<ul style="list-style-type: none"> <li>• Reduction in costs and lost production through illness</li> </ul>
<b>Academia</b>	
Researchers	<ul style="list-style-type: none"> <li>• A framework within which to bid for work in priority areas and to establish collaborations (national and international)</li> <li>• An information source to facilitate definition of competitive and relevant R&amp;D programmes</li> <li>• A better infrastructure including top-notch technological equipment</li> </ul>
<b>Research Councils &amp; other funding bodies</b>	<ul style="list-style-type: none"> <li>• A framework within which to gain an overview of current research programmes, avoid duplication and gain cross disciplinary and cross institutional synergy</li> </ul>
<b>General public</b>	<ul style="list-style-type: none"> <li>• Increased awareness of diseases, their symptoms and consequences</li> </ul>
<b>Charities</b>	<ul style="list-style-type: none"> <li>• Improved quality of life for diseases of interest</li> </ul>

**Figure 6. Benefits to stakeholders**

## Contributions to standards

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InnoMed will not contribute to international standards *per se* but the InnoMed project will evaluate a new approach to drug discovery and development. Its potential to change the biopharmaceuticals research and development process is based on a more systematic use of biomarkers and on leveraging highly innovative technologies such as 'omics technologies and other types of data in combination with appropriate biostatistical models. However, it is foreseen that the results gained will provide input to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

If the use of biomarkers is generalized for preclinical and clinical investigations, the InnoMed project will contribute through intensive discussions with the regulatory authorities to a new approach to evaluate risk and benefit for the patient. This approach will also favour cross-functional collaboration between pre-clinical and clinical scientists and promote translational medicine.

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

## Abbreviations

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DB	Database
EBE	Emerging Biotechnology Enterprises
EC	European Commission
EFB	European Federation of Biotechnology
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPF	European Patients Forum
ETP	European Technology Platform
EU	European Union
EUFEPS	European Federation for Pharmaceutical Sciences
GDP	Gross Domestic Product
GLP	Good Laboratory Practices
IP	Integrated Project
IPRs	Intellectual Property Rights
IT	Informational Technology
NIEHS	US National Institute of Environmental Health Sciences
R&D	Research and Development
RDG	Research Directors Group
SME	Small Medium Enterprise
SRA	Strategic Research Agenda