

# Innovative medicines for Europe\*

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**The Joint Technology Initiative for Innovative Medicines for European Citizens is proposed within the context of the European Commission's proposals for the Seventh Framework Programme (2007-2013) and proposes clear practical paths to accelerate the development of safe and more effective approved new medicines. This will be achieved by stimulating integrated forms of co-operation in research and development, in particular through a public-private partnership (PPP), to be established especially for this purpose. This will become operational in 2007 and current calculations forecast investments of approximately €440 million per year.**

## Introduction

Because the European pharmaceutical industry is lagging seriously behind its competitors, mainly in the US, and seems to be particularly slow in harnessing the benefits of the revolution in biotechnology, the European Commission requested the Research Directors' Group of the European Federation of Pharmaceutical Industries' Associations (EFPIA) to identify the main barriers to innovation in Life Sciences research in Europe with the objective of establishing a new initiative for Innovative

Medicines. This is because one of the major objectives of the European Union is to build the most competitive and dynamic knowledge-based economy in the world by 2010, a key element of which is to strengthen the science base in Europe. In this context, the biopharmaceutical environment is characterised particularly by its focus on science and innovation. It is therefore essential to revitalise this environment so as to make it become more competitive, not by fast-tracking the production of new compounds, but more

by a root and branch review of the entire pharmaceutical R&D process. This "bench to bedside" approach would entail the development of a new "toolbox", developed through collaboration between all stakeholders (patients, industry, including the SME sector, regulators, clinical and academic researchers, etc.), that would constitute the means to streamline the R&D process and thereby ensure that patients obtain new medicines faster without compromising safety.

The development of a new drug is a long, resource intensive and complex process. The overall cost for just one compound is estimated to be €868,000,000 at prices for the year 2000.<sup>1</sup> The possibility of failure to reach the market by the end 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>2</sup> Improving these odds depends upon a concerted research effort to overcome the perceived bottlenecks in this R&D development pathway so as to bring more efficacious and safer drugs to the market more quickly, resulting in a direct benefit for patients.

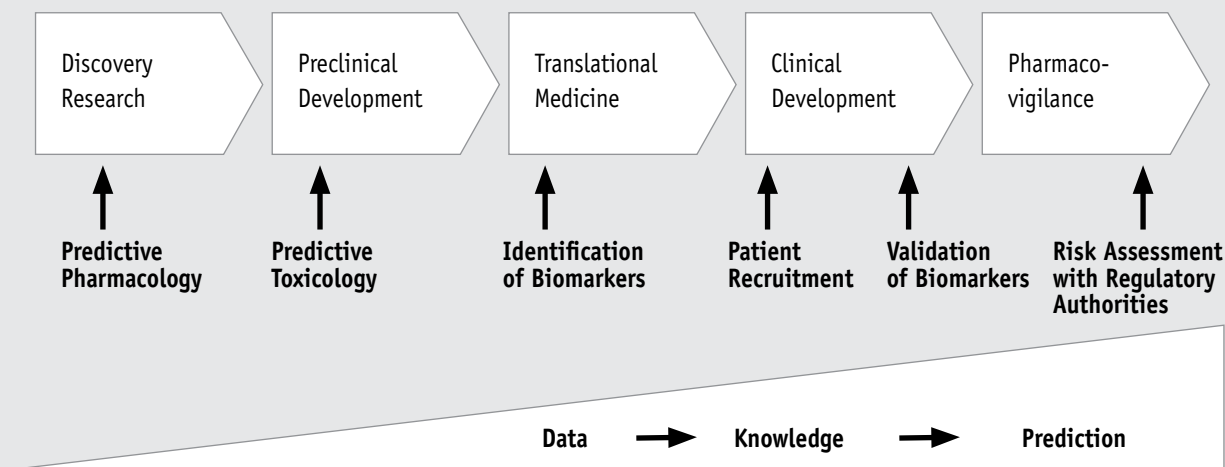
The greatest need for the pharmaceutical industry is to detect the possibility of failure at the earliest stage as possible, and it is in this context that advances in basic biomedical science within the European research community could make the greatest contribution.

At the same time, the European Commission also developed the Joint Technology Initiative concept as a means of identifying and resolving major economic, technological or societal challenges that have Research and Development aspects. These will generate effective public-private partnerships between all relevant stakeholders, whether they are companies, research institutions, the financial world and 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. Joint Technology Initiatives are expected to contribute to achieving the

\*The opinions expressed in this article are of the author and do not, necessarily, represent the official views of the European Commission.

Figure 1

**R&D Processes in drug development**



Source: EFPIA

objective for Europe of becoming "...the most competitive and dynamic knowledge-based economy in the world capable of sustainable economic growth with more and better jobs and greater social cohesion". This is referred to as the Lisbon objective, which amongst others, aims to improve the research climate in Europe in terms of better growth and competitiveness and increasing investment in R&D towards the 3% of overall European GDP. 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>3</sup>

Clearly, a Joint Technology Initiative for Innovative Medicines was the answer.

With this in mind, industry responded by identifying 4 areas for action in agreement with key stakeholders:

- Better prediction of safety
- Better prediction of efficacy
- Knowledge management
- Education and training

Through a series of several workshops involving over 300 experts in research and development representing all stakeholder groups (academia, large pharmaceutical

industries, the SME sector, regulatory agencies including the European Medicines' Agency, patient organisations and financial institutions) were consulted and came to the following conclusions on each of the above issues.

**Better prediction of safety**

Pre-clinical safety, or toxicological issues are responsible for 20% of the overall attrition rate for candidate medicinal products in pharmaceutical development. There is greater public and media scrutiny of pharmaceuticals and regulatory decision-making than before and a perceived overall weakness of the post-marketing surveillance system. Regulatory authorities have accordingly become more risk-averse, requiring ever broader and more restrictive risk management strategies to avoid such problems, with the need for expanded studies to quantify potential serious adverse events, even those of great rarity or scientific improbability. There is an increasing tendency for the approval of more restricted indications (with requests for increased data for broader indications) slowing down approval for marketing and delayed patient access to innovative medicines that address medical needs.

The following suggestions from the consulted experts are intended to enhance this overall process:

- Create a European Centre of Drug Safety to identify and co-ordinate research needs in safety sciences, including the development of a pan-European Safety Sciences Programme
- Establish a framework for biomarker development which will evaluate human relevance and regulatory utility
- Develop in silico methods for better prediction of safety
- Study the relevance of rodent non-genotoxic carcinogens
- Tackle intractable toxicity
- Improve healthcare provider training in detection of adverse drug reactions
- Development of databases including knowledge management tools of data analysis in pharmacovigilance
- Improve communication between patients, physicians and other healthcare providers in pharmacovigilance

Greater use will need to be made of in-silico tools and newly emerging disciplines such as toxicogenomics<sup>\*</sup>, toxicoproteomics<sup>†</sup> and metabonomics<sup>‡</sup> in

\* The collection, interpretation, and storage of information about gene and protein activity in order to identify toxic substances in the environment and to help treat people at the greatest risk of diseases caused by environmental pollutants or toxicants

† The use of global protein expression technologies to understand better environmental and genetic factors, both in episodes of acute exposure to toxicants and in the long-term development of disease

‡ Used interchangeably with "metabonomics", signifying the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification

an integrated fashion so as to get a better idea and sooner of a candidate compound's chances of making it to market.

### **Better prediction of efficacy**

A number of issues emerge as suitable and necessary for action:

#### **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".<sup>4</sup> They can be used as tools to understand the biology of a disease but also to understand the effects of a new drug sooner than at present. This can result in better and earlier decision-making about whether to proceed with the development of a compound, reducing late-stage and more costly attrition. This could mean benefits such as : increasing the probability of program success and reduced cycle times, matching patients with therapy; faster optimisation of therapy; improved compliance with therapy, reduced complications of therapy and disease, more efficient drug development, more efficient healthcare delivery and ultimately reduced societal healthcare burden.

#### **Patient involvement**

This is perhaps the most important part of the medicine development process and consumes over 50% of the time available. One of the major components is the patient recruitment phase which can last on average twelve months if not longer. Reducing its duration will have a substantial effect on the time needed to develop new medicines provide a competitive edge in terms of performing clinical trials. A potential means of achieving this could be through education of patients about the benefits of participating in research. They should not only be informed about the outcome of the clinical research but also be involved in the design of the study. This is important for developing a more patient-oriented approach to treatment and for their participation in an educational process involving not just them, but also carers and researchers to ensure best treatment outcomes. Issues to be resolved include

the precarious nature of their funding, the establishment and maintenance of patient records and databases of information and quality of life measurements as outcomes to clinical trials that identify most closely with their experiences.

#### **Regulatory approvals**

As final judge of the risk/benefit ratio for each new application, regulatory authorities are most sensitive to public concerns about medicines as reflected in expanded requirements to outrule the possibility of serious and other adverse events. This can result in serious delays in obtaining marketing authorisations for new medicines to redress medical needs and the following items have been identified as suitable for action:

- Improved dialogue with regulators during drug development prior to regulatory approval so as to reduce requests for additional data following submission,
- Increased acceptance by regulatory authorities of biomarkers and surrogate clinical end points to clinical trials,
- Increase the involvement of other stakeholders, especially patients, in the regulatory review process,
- Develop methodologies for data collection on the risks and benefits of medicines once they are available in a real world setting,
- Ensure appropriate use of the conditional approval process for innovative new medicines with an adequate safety profile,
- Develop with regulators proposals to increase sharing of data, for example on the placebo arms of clinical trials,
- Encourage discussion on a more flexible approach to clinical trials that reflects the individual needs of particular disease areas, e.g. quality of life issues that identify closely with patient needs

Other recommendations are as follows :

- Develop better understanding of disease mechanisms,
- Develop in vitro and in vivo models predictive of clinical efficacy,
- Develop in silico simulations of disease pathology,
- Create disease-specific European Imaging Networks,

- Create disease-specific European Centres for validation of omics-based biomarkers,
- Co-ordinate the development of national patient networks,
- Form European consortia to address value demonstration,
- Develop a framework in partnership with the regulators for innovative clinical trial design and analysis.

#### **Knowledge management**

The vast sources of scientific and technical knowledge that need to be linked together under the auspices of the Joint Technology Initiative for Innovative Medicines are extremely diverse with regard to origin, availability, ownership, scientific content and many other features. This diversity, the complexity of underlying science and the means of drawing meaningful conclusions from them are also likely to increase with time.

It must therefore be asked what information is needed (and what is not needed) from such information sources, what tools are need to extract such information, how can it be analysed in such a way that will enable meaningful conclusions to be drawn from it so as to enable accurate predictions to be made that are relevant to real-life situations. The following issues need to be borne in mind.

Firstly and from the users' point of view, the knowledge management system must reflect the way those who utilise it (here : the biopharmaceutical community stakeholders as mentioned above) work together and it must integrate smoothly in their day-to-day environment. In particular, it must provide relevant, simple and intuitive access to various information sources and yet be capable of organising it according to content, allow for data to be integrated or pooled, analysed and constructed into models that reflect real-life situations. Examples include tasks as simple as identifying a clinical expert with a particular profile or as complex as pooling together the placebo arms of several clinical trials into one large pool that can serve as one virtual half of a clinical study versus a comparator product. It should also allow for issues such as virtual meetings, knowledge sharing, forums, discussions, etc., open to whole community, as well as within context-

defined sub-communities.

From the technical point of view, the key objective is to ensure seamless data integration across a broad range of heterogeneous scientific, computer and other technical resources across differing organisations and networks. Further, it should be adaptable enough to be based upon existing and emerging data representation standards and yet be able to satisfy unpredictable requirements as they emerge.

From this seemingly impossible set of requirements, only the broadest recommendations can be made and these appear to be as follows:

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

In principle, the required flexibility of the future platform can be met by designing a federated environment based on existing stand-alone tools, components and resources, based on open common architectural standards that can be adapted to contemporary needs and capable of dynamic reconfiguration.

## Education and training

The goal of education and training activities associated with the Joint Technology Initiative for the Innovative Medicines Initiative should be to support the interdisciplinary education process essential to the bioscience sector. This entails the development of a new concept referred to as "Translational Medicine" or Translational Science", which may be defined as:

*"...a comprehensive European-based approach aimed at a common understanding throughout all relevant scientific disciplines of the research and development steps that bring a new biochemical substance or technique (NCE, biotechnological intervention, etc.) to market as a therapeutic clinically safe and effective intervention."*

This will require the establishment of a pan-European platform responsible for the education and training of current and future professionals involved in the biopharmaceutical research and development process, including lifecycle management. It will need to be based upon existing centres of excellence within the disciplines and therefore not be a new or parallel entity.

Its main priorities will be as follows:

- To act as a central coordinating unit and an advisory education and training council
- To develop programmes for integrated medicine development, ethics committees and patient organisations,
- To develop programmes for safety scientists within pharmaceutical R&D
- To develop Regulatory Affairs-based programmes
- To develop appropriate training programmes for biostatisticians, bioinformaticians and biomedical informaticians
- To develop programmes for pharmaceutical medicine professionals

Patients and their representatives should be involved as far as possible since they can make a key contribution to the determination of what and how the professionals acquire skills and knowledge of greatest use to the public. Furthermore, there is a need for ongoing training for experts, or what is referred to as Continuous Professional Development, to keep up to date with developments in science and technology. This will entail the training of specialists to acquire knowledge from areas other than those they graduated from, e.g. business and finance training for clinical scientists working, for example in the SME sector.

Following a consultation process with relevant stakeholders, a number of gaps will need to be filled in the Education and Training process that fall under the following headings:

- Increased scientific interaction, in terms of information and personnel, between the academic world and industry and regulatory authorities on the other, to facilitate the sharing and exchange of knowledge. In most European

countries this is characterised mainly by a brain-drain to industry, mostly for financial reasons.

- Safety scientists with a much broader spectrum of knowledge drawn from areas such as primary and secondary pharmacology, functional genomics, safety pharmacology, physiology, pathophysiology, physical chemistry, animal and clinical toxicology, cellular biology, biochemistry and animal physiology,
- Clinical pharmacologists, non-clinical and clinical,
- Physicians specialised in pharmaceutical medicine,
- Specialists in bioinformatics, biostatistics, systems pharmacology and physiology (in vivo whole organism), medical imaging and in-silico modelling,
- Regulatory personnel trained in disciplines arising from the Clinical Trials (GCP) Directive,<sup>5</sup> namely inspectors, clinical investigators, monitors, clinical research associates and members of ethics committee.
- A better understanding of the process of medicines development to be communicated to journalists, venture capitalists and the general public.

The success of these measures will depend on the support from all relevant stakeholders, especially the European biomedical industry, academia, scientific and professional societies, patient groups, regulatory bodies and the European Commission. Minimal bureaucracy will be the key to ensuring maximum flexibility and rapid action.

## Legislative developments

The first and most important of these is Regulation (EC) 726/2004,<sup>6</sup> which governs the European Regulator, the European Medicines' Agency (EMA) as well as the scope of the centralised marketing authorisation procedure. Up to recently, this has been a requirement for products derived from biotechnology and optional for new chemical entities. Centralised assessment is now compulsory for products intended for use in the treatment of AIDS, cancer, neurodegenerative disorders and diabetes mellitus. From May 20, 2008, this will be

extended to cover products used to treat autoimmune diseases and other immune dysfunctions, as well as viral diseases. As a consequence, many more new products will be assessed via this method.

Three new marketing authorisations have also been introduced: accelerated authorisation, compassionate use and "exceptional circumstances". The accelerated procedure (6, art. 14)<sup>9</sup> comprises a 150-day review as opposed to the usual 210 days and covers products, which represent a major public health or other therapeutic interest. This was first developed by the EMEA in 2001 so as to expedite the review of marketing authorisation applications for life-threatening or incapacitating disorders. In order to be evaluated under this process, a product must be indicated for a serious disease, it must be the only possible treatment and it must possess exceptionally high therapeutic benefit.

"Exceptional circumstances" (6 art. 14)<sup>8</sup> refers to approval for marketing of products where comprehensive information cannot be provided by the applicant (small study size due to the overall rarity of the condition e.g. in certain orphan indications), or where collecting such data would be contrary to accepted medical ethics. Such products would be available by prescription only, be subject to strict medical supervision and their package leaflets would have to be formulated in such a way as to draw attention to the fact that many particulars concerning the product are as yet unavailable or inadequate.

"Compassionate use" (6, art. 83),<sup>7</sup> refers to a specific provision that remains to be introduced, which will be complementary to national legislation and will provide an option to Member States who wish to receive a CHMP opinion regarding the conditions for compassionate use of a specific medicinal product which falls within the scope of the regulation.

Each of the following specific criteria should be fulfilled:

- The medicinal product is to be made available to patients with a chronically or seriously debilitating disease, or a life threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product in Europe,

- The compassionate use programme is intended for a group of patients,
- The medicinal product is either the subject of an application for a centralised marketing authorisation or is undergoing clinical trials in the European Union and/or elsewhere.

A Conditional Marketing Authorisation,<sup>8</sup> separate from other foregoing legal provisions, is also planned which allows for a product to be granted temporary approval under Regulation 726/2004<sup>6</sup> for one year only and subject to annual review by EMEA. In particular, full clinical data will have to be provided post-approval, but the applicant will still have to provide full preclinical (animal) information at the time of application as well as demonstrate a positive benefit/risk ratio of the drug. This is intended for orphan medicinal products and products intended for rapidly arising public health threats.

Pharmacovigilance and post-marketing surveillance receive greater attention. This places even greater emphasis on the continuous monitoring of the risk/benefit ratio of marketed products on an ongoing basis, taking account of all post-approval safety information. Marketing Authorisation Holders will be required to have "permanently and continuously at [their] disposal" a person appropriately qualified in pharmacovigilance. This person is responsible for managing pharmacovigilance systems and in particular, the submission of pharmacovigilance or Periodic Safety Update Reports (PSURs) to the competent authorities, which will follow a tighter timetable than before. These will have to be submitted every 6 months after approval until the product is marketed. After this has started, PSURs must be submitted every 6 months for the first two years, then once a year for another 2 years and at 3-yearly intervals thereafter. Regulatory authorities will be allowed to request a PSUR at any time at their discretion.

Directive 2004/27/EC,<sup>9</sup> which amends the Community Code on medicinal products for human use, foresees a number of important changes, the most important of which are as follows:

- The decentralised approval procedure, which operates alongside the mutual recognition procedure and whereby a reference member state issues its own assessment report on a proposed new product. This is circulated to other Member States, who can issue their own marketing authorisations on this basis,
- A global Marketing Authorisation, which covers all future forms, strengths, routes of administration, extensions and variations to a product. This will limit the ability of generic pharmaceutical companies from making minor changes to Marketing Authorisation Applications,
- Definition of a generic product as that with the same quantitative and qualitative composition as a reference product and that has been shown to be bioequivalent to this product. This necessarily includes all salts, esters, isomers, complexes and derivatives of that substance, unless they differ in terms of efficacy and/or safety,
- Similar biological medicines, or "biosimilars", regarded as "comparable" versions of biological drugs. This lays down a clear and firm legal pathway for their registration and is complemented by scientific guidelines from the EMEA,
- Sunset clause, whereby the marketing authorisation of product not placed on the market within three years of the date of its date of issue can be withdrawn. Companies will therefore be required to notify the regulatory authorities when they market a product,
- Market exclusivity is harmonised throughout the EU, whereby each newly approved drug benefits from eight years data exclusivity. This is extended by a further two years, during which generic versions may not be placed on the market, but can nevertheless be developed, submitted and authorised without infringing the originator's patent rights. Marketing can only commence after expiry of this period, or one year later again, if within the first eight years, a product gains a new indication deemed to be of "...significant clinical benefit in comparison with other therapies".



## Small and medium-sized enterprises (SMEs)

One of the more innovative provisions of the new legislation package is the range of incentives offered to the small- and medium-sized enterprise sector operating in the field of pharmaceuticals. Under the terms of the legislation, considerable savings can be made in the seeking of various degrees of scientific advice and inspection fees at EMEA by reductions of up to 90% and the deferral of payments for such advice until after successful authorisation of products.

According to the terms of Commission Recommendation 2003/361/EC,<sup>10</sup> a small- or medium-sized enterprise is defined as one with fewer than 250 employees, an annual turnover not exceeding €50m and a balance sheet not exceeding €43m. A **small enterprise** has fewer than 50 employees, an annual turnover/annual balance sheet not exceeding €10m and a **micro** enterprise has less than 10 employees with an annual turnover/annual balance sheet of less than €2m.

To determine which companies are eligible for SME incentives, the EMEA will apply the definition of micro, small and medium-sized enterprises provided in this recommendation.

The main provisions of the legislation are as follows<sup>11</sup>:

- Administrative and procedural assistance from the SME Office at EMEA,
- Fee reductions for scientific advice, inspections and (for veterinary medicines) establishment of maximum residue limits,
- Fee exemptions for certain administrative services of the EMEA,
- Deferral of the fee payable for an application for marketing authorisation or related inspection,
- Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful,
- Assistance with translations of the product information documents submitted in the application for marketing authorisation.

A responsible and especially dedicated office has been established at the EMEA for the submission of requests for designation of SME status and to answer further queries.<sup>12</sup> A comprehensive guide has been published giving further information.<sup>13</sup>

## Seventh framework programme

It is intended that the Joint Technology Initiative for Innovative Medicines will be an integral and yet autonomous part of the Seventh Research Framework Programme.<sup>14</sup> In this, collaborative research will constitute the bulk and the core of EU research funding. The objective is to establish, in the major fields of advancement of knowledge, excellent research projects and networks able to attract researchers and investments from Europe and the entire world.

Within the health domain, the primary concern remains to improve the health of European citizens while at the same time to increase the competitiveness of European health-related industries and businesses. Emphasis will be put on bringing the fruits of research to market as soon as possible in the form of safe and effective clinical applications, new therapies, methods for health promotion and prevention, diagnostic tools and technologies, as well as sustainable and efficient healthcare systems.

Activities extend to three 3 main areas :

- Biotechnology, generic tools and technologies for human health, including research in molecular screening, diagnostics, alternatives to animal testing
- Translating research for human health, including ageing, brain diseases, infectious diseases and major diseases
- Optimising the delivery of healthcare to European citizens, comprising more efficient use of health care interventions

All activities will be carried out in pursuit of the general objectives described in Article 163 of the Treaty in contributing towards the creation of a knowledge-based society, and to build on a European Research Area for all European citizens.

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