

## 2 Improved Predictivity of Drug Safety Evaluation

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### 2.1 Summary

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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 6<sup>th</sup> 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

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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 toxicities<sup>29</sup>.

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 6<sup>th</sup> 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.

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<sup>29</sup> 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<sup>30,31</sup>. As with the impact of adverse drug reactions, annual mortality varies from country to country (10,000 deaths in the UK,<sup>32</sup> 100,000 in the USA<sup>33</sup>). 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 administration<sup>34</sup>.

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 interventions<sup>35</sup>.

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.

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

<sup>31</sup> Woodcock J. et al. JAMA 1999; 281:1728-1734

<sup>32</sup> Pirmohamed et al. BMJ 2004; 329; 15-19

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

<sup>34</sup> WHO 2002. The importance of Pharmacovigilance Safety monitoring of medicinal products ISBN 9241590157

<sup>35</sup> 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<sup>36,37</sup>.

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 7<sup>th</sup> 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

<sup>36</sup> Smalley W. et al. JAMA 2000; 284: 3036-3039

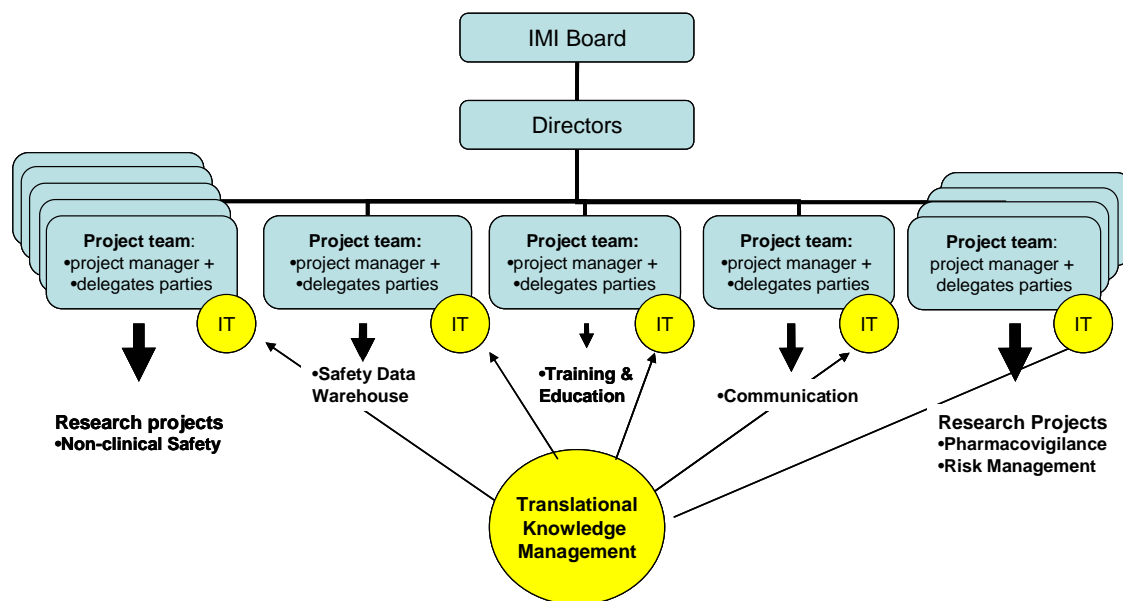
<sup>37</sup> Graham D.J. et al. JAMA 2001; 286 No. 7: 831-833

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

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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.

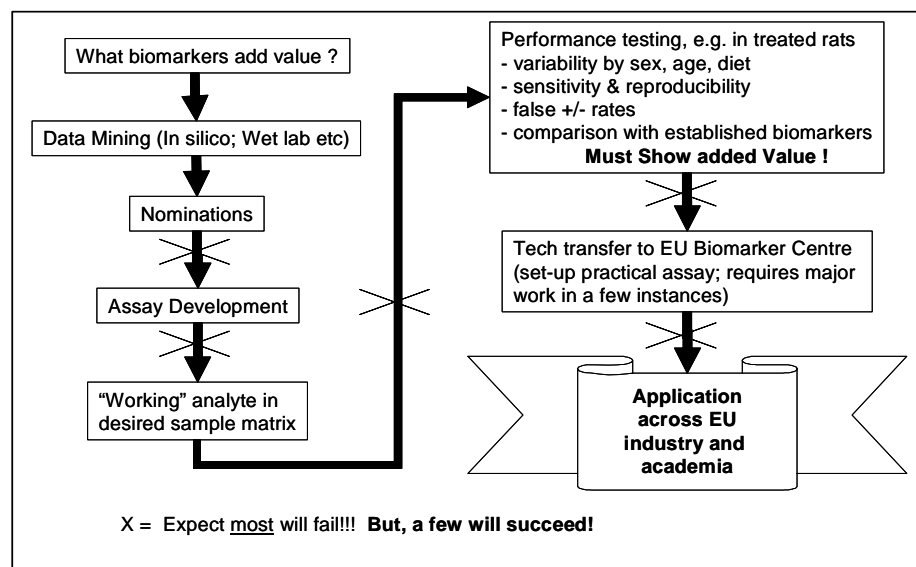
The purpose of the project is to clarify the utility and human relevance of these candidate biomarkers and, in consequence, their regulatory value.

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, Reprotect 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

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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.

<b>Activity</b>	<b>Costs per year (€mn)</b>
<b>European Center of Drug Safety Research (ECDSR)</b>	<b>36.7</b>
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
<b>Biomarker Development</b>	<b>22.5</b>
Project Support	3.0
Project Costs (8 projects)	12.0
Extension of FP6 project	7.5
<b>Relevance of Non-genotoxic Carcinogenicity</b>	<b>22.5</b>
50 Post Docs	7.5
Project Costs (30 studies)	15.0
<b>Clinical Safety and Pharmacovigilance</b>	<b>68.7</b>
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
<b>IT Infrastructure and support</b>	<b>15.0</b>
<b>TOTAL (€mn per year)</b>	<b>165.4</b>

## 2.7 List of Contributors

### 2.7.1 Non-clinical Safety

<b>Non-clinical Safety</b>			
<b>Stakeholders Group</b>	<b>Last Name</b>	<b>First Name</b>	<b>Institution</b>
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## 2.7.2 Pharmacovigilance and Risk Management

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