IMI Joint Undertaking - Scientific Priorities for 2008

1. Improve Predictivity of Immunogenicity

Immunogenicity is key to development of biotherapeutics, since it affects safety, efficacy and interpretation of study data. There is a need to predict and minimize immunogenicity in man but there are major unresolved issues. There is limited comparability of immunogenicity data between assays. Factors or patterns favouring immunogenicity are not well understood and there is a lack of reliable prediction methods for immunogenicity and its clinical consequences. Currently there is no possibility to stratify patients according to their susceptibility to develop immune responses. The project encompasses finding ways to make immunogenicity analysis comparable between assays, compounds and companies and gain insight based on pooled relevant immunogenicity data. The predictive value of pre-clinical tools (*in silico*, *in vitro*, animal models and stratification markers) will be investigated and shared. Contact will be maintained with relevent activities elswhere.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €13m.

2. Non-genotoxic carcinogenesis

Tumour findings are common endpoints in the preclinical testing of drug candidates in rodent models. Such *in vivo* carcinogenesis is rarely genotoxic in nature, as directly genotoxic compounds are excluded at an early point in the drug development process by use of *in vitro* and *in vivo* assays. However, there exist no sufficiently accurate and well-validated short-term assays to identify non-genotoxic carcinogens, thus necessitating an expensive 2-year rodent bioassay for assessing the carcinogenic risk of such compounds to humans. It would be exceedingly valuable to establish the mechanisms by which early biomarkers are linked to tumour formation, and ultimately demonstrate the concept that early biomarkers can reliably and robustly predict later cancer development, including potential insight into the human relevance of rodent non-genotoxic carcinogens. This project is for a 2-year "Exploratory Phase" during which the focus will be on evaluating the utility of new experimental models and tools. A decision will be made at the end of this period to continue into a 3-year "Confirmatory Phase" for validation and clinical translation.

Duration 2+3 years
Indicative total in-kind contribution from the EFPIA companies €2.5m (Exploratory), €10m (Confirmatory).

3. Expert systems for *in silico* toxicity prediction

In vivo studies often unveil side effects of drugs which presently cannot be predicted from the chemistry of the molecule. However, mechanisms such as cross-target activation or inhibition, or straight chemistry-linked toxicities are amenable to prediction. Early *in silico* prediction of such cases would increase the quality of drug candidates and ensure a lower attrition rate before and during the first GLP animal studies. The project will collect pharmacology-related chemistry ("molecule war-heads") from known series to build up predictive expert systems for secondary pharmacology ("off-target toxicity") prediction. The same approach will be used for pure chemistry-related toxicity (e.g., cationic amphiphilic drugs and phospholipidosis). The project will exploit legacy preclinical reports from the pharmaceutical industry to link chemical features to pathology findings and extract patterns for *in silico* prediction.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €5m.

4. Improved predictivity of non-clinical safety evaluation

The goals are to assess the value of combining results from 'omics technologies together with the results from conventional toxicology methods for more informed decision making earlier in preclinical safety evaluation. In this context, identification and qualification of novel translational biomarkers of selected toxicities in relevant species for use in non-clinical safety studies will be undertaken. The relevance of this approach is closely linked to acceptance of new biomarkers by Regulatory Authorities. The final goal will be to integrate new, validated methods into non-clinical safety assessment. The research programme will consist of performance of *in vivo* animal studies based on standardized and optimized study protocols, mainly in rats but also selectively in non-rodent species, using well characterized drug candidates from participating companies and reference compounds selected on the basis of liver or kidney toxicity.

Duration 3 years
Indicative total in-kind contribution from the EFPIA companies €10m.

5. Qualification of translational safety biomarkers

A lack of specific and sensitive mechanistic safety markers and their respective assays for human samples is regularly delaying drug development programmes. Furthermore, the predictivity between non-clinical and early clinical studies of currently accepted markers is very poor. There is no clear scientific qualification process on how to generate enough clinical evidence (and potentially supporting pre-clinical evidence) to qualify new safety biomarkers for clinical regulatory decision making in certain contexts. It is very important to cooperate in the definition of such a generic scientific process, which needs to match the regulatory qualification processes recently proposed by the health authorities, and to test several options before one could be accepted by all parties. Three target organs will be selected as examples of critical

drug-induced pathologies (liver, kidney and vascular) and a subset of markers will be identified from previous discoveries and/or other pre-clinical qualification exercises and their assays developed for human use if not yet available. The selection of the markers will be based on their potential/probable success of becoming a useful translational tool.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €21m.

6. Strengthening the monitoring of the benefit/risk of medicines

The project will facilitate the application of existing data resources and/or expedite the generation of more, and more reliable, pharmacoepidemiological data for proactive pharmacovigilance and risk management of medicines throughout their life-cycle. Work will be directed towards developing, implementing and/or evaluating new methodologies in pharmacovigilance and pharmacoepidemiology, e.g. signal identification/detection, data mining based on large safety databases, integration of drug utilisation information into pharmacovigilance and/or post-approval benefit: risk optimisation. Work will also focus on establishing and working to common standards, protocols and terminologies to ensure both transparency and uniformity in the conduct and reporting of studies in this field. Training aspects will also be addressed where appropriate. The project will aim to establish EU-wide pharmacoepidemiology and pharmacovigilance collaborations and networking, and to harmonise health care databases and patient registries.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €15m.

7. Islet cell research

While several tissues are implicated in the progression of insulin resistance to type 2 diabetes, the latter will not occur if pancreatic islet β-cell mass and function are maintained. Significant β-cell dysfunction occurs prior to diagnosis of insulin resistance. Current treatments are not able to prevent the continued loss of β-cell mass and function and progression to type 2 diabetes. In both type 1 and type 2 diabetes, hyperglycaemia results from the inability of ß-cells to adapt their functional mass to the prevailing insulin demand. However, the mechanisms leading to these alterations are poorly understood. A better understanding of β-cell proliferation, differentiation and apoptosis will permit the identification of approaches to preserve ß cell function. This will foster the development of preventive and curative treatments for both type 2 diabetes and type 1 diabetes. The project will focus on molecular, physiological and clinical aspects of ß-cell function and turn-over, regulation and diagnostics.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €10m.

8. Surrogate markers for vascular endpoints

A majority of patients with either type 1 or type 2 diabetes will have either micro- or macrovascular complications or both after several years of disease. Microvascular complications may occur in the eye (retinopathy), kidney (nephropathy) or in the nerves (neuropathy). The most common macrovascular complication is atherosclerosis, which can lead to problems such as myocardial infarction or stroke. The factors that contribute to these complications are not well understood. There is a need to develop ways to reduce the size and timelines for evaluating therapeutic efficacy on the establishment/ progression of micro and/or macrovascular complications. Therefore the project aims to find validated and scientifically justified biomarkers /surrogate endpoints for micro- and macrovascular hard endpoints in diabetes clinical research. A lack of animal models which can predict the development of diabetic micro- or macrovascular disease is also a major issue in the development of novel therapies and the project will aim to develop and validate new *in vitro* or *in silico* tools to test novel therapies.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €20m.

9. Pain research

The management and treatment of pain remains unsatisfactory. Existing treatments for chronic pain provide incomplete relief for some patients or carry a side-effect profile that is unacceptable. This project aims to improve our understanding of the pathways and mechanisms mediating different kinds of pain, to develop translatable efficacy, pharmacodynamic (PD) and pharmacokinetic measures in animals and humans, to establish and validate mechanism-based human pain models, and to develop robust markers for patient stratification and quantitative pain assessment, so that potential novel analgesics can be efficiently tested and compared in relevant patient groups.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €7.5m.

10. New tools for the development of novel therapies in psychiatric disorders

The pathophysiological processes and etiologic factors in depression and schizophrenia have so far proven elusive. Despite a growing understanding of the genetic and biochemical determinants resulting in the development of these disorders, development of safe therapies that effectively relieve the core symptoms or delay the progression of the diseases remains a challenge. The development of preclinical models with sensitive pharmacodynamic markers that are closely linked to the pathophysiology of the disease is essential to improve the validity of preclinical models. This project focuses on development of platforms that translate efficacy of therapeutic approaches within these disorders into blood/CSF markers, or imaging

and/or electrophysiological measures suitable for clinical assessments. The objective will be to leverage expertise in both disease areas for mutual gain.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €10m.

11. Neurodegenerative disorders

Clinical outcome studies in the neurodegeneration area are notoriously long and expensive. In order to accelerate the successful development of molecules for the treatment of neurodegenerative disorders, it is essential to improve the predictive value of animal models, identify pharmacodynamic markers of drug response, and develop pharmacodynamic models that allow early prediction of efficacy and markers to aid stratification of the patient population. The project requires the integration of preclinical and clinical science to ensure effective translation of efficacy from bench to bedside and visa versa. The project focuses on the development of translatable animal and human volunteer models predictive of clinical efficacy in patients in the areas of Alzheimer's disease, Parkinson's disease and multiple sclerosis. One long-term objective will be to exploit similarities in these diseases to develop models that support clinical development across all three diseases.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €7.5m.

12. Understanding severe asthma

Despite the availability of effective treatments for patients with mild to moderate disease, there is a high unmet need for more effective, convenient and safe therapies for patients with severe disease. Discovery, research and development of new treatments for patients with severe asthma presents clear challenges. There is a need for effective use and further development of diagnostic criteria for mechanistic and therapeutic trials. Without better understanding of disease etiology and pathogenesis, relevant preclinical and clinical models cannot be developed to enable translational research strategies. This project aims to build an EU Severe Asthma consortium focussed on disease understanding. The consortium will set up a large longitudinal patient cohort that will enable research to validate novel biomarkers and clinical measures, and will serve as a vehicle for devloping translational models.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €12.5m.

13. COPD patient recorded outcomes

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease resulting in progressively increased fixed airflow obstruction and widespread structural and functional abnormalities also in the surrounding lung parenchyma**.**

Demonstration of efficacy of new therapy has relied on showing reduction of airflow obstruction. There is now a clear understanding that this does not capture the potential benefits that the patient experiences. Capturing the COPD patients' experience of the disease and effects of treatment is an important aspect of evaluating treatments for COPD. The project will consist of two phases; the first to develop a framework to understand the patients' experience of COPD that will inform strategies for measuring meaningful outcomes in clinical trials; the second to develop a PRO measurement tool for use in clinical trials to evaluate treatments.

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Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €10m.

14. European Medicines Research Training Network

The pharmaceutical industry needs highly skilled professionals who understand cutting edge technologies and life science disciplines to perform and deliver their research and development. Industry also needs the ability to support the continued professional development for pharmaceutical employees who often have to re-skill in a rapidly moving business. This project will establish a pan-European platform of excellence for education and training (E&T) in the biopharmaceutical field, covering the whole lifecycle of a medicine from research to pharmacovigilance. The aim is to create a sustainable academia-industry cross-disciplinary approach to facilitate collaboration on education & training, to anticipate emerging needs and provide appropriate training solutions. The project will create a network to identify and explore options for responding to these needs and pave the way for a European Biopharmaceutical Research Training platform able to efficiently organise training courses on emerging science and technologies that can be made rapidly available across Europe.

Duration 7 years
Indicative total in-kind contribution from the EFPIA companies €5m.

15. Safety sciences for medicines training programme

Safety scientists with a much broader spectrum of knowledge than the traditional toxicologist are much needed. The future safety scientist will have to integrate knowledge accumulated from many safety-relevant disciplines (for example primary and secondary pharmacology, drug metabolism & kinetics, functional genomics, safety pharmacology, mammalian anatomy, embryology and physiology, patho-physiology, physical chemistry, animal and clinical toxicology, cellular biology, biochemistry, with all their specialist branches) if they are to excel in modern risk assessment and risk management. The safety scientist should bridge from classical pharmaceutical toxicology to human safety pharmacology. This project will establish a programme to train scientists holding a degree in life sciences to become knowledgeable in the fields necessary to perform a holistic evaluation of the safety of a new medicine by evaluating and linking animal and human/patient safety data.

Duration 5 years

Indicative total in-kind contribution from the EFPIA companies €3m.

16. Pharmaceutical medicine training programme

Pharmaceutical Medicine is a medical scientific interdisciplinary field concerned with the discovery, development, evaluation, registration, monitoring and medical aspects of marketing of medicines for the benefit of patients and public health. There is a need to improve the professional effectiveness of physicians and other life science graduates by promoting education and training in pharmaceutical medicine throughout the European Union. This is to be accomplished by the harmonised activity of existing and new courses. A network of academic centres will be established that will deliver foundation and advanced postgraduate training programmes, employing state of the art educational methodology to include quality management of the processes and outcomes. External validity and appropriateness of the contents, as well as practical applicability of the training programmes will be ensured.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €4m.

17. Integrated medicines development training programme

An integrated overview of the medicines development process, including ethics, scientific methodology, regulatory requirements, assessments of risk and benefit, intellectual property matters, business skills and understanding of the business environment is needed by many stakeholders who are involved to greater or lesser extents in the process of medicines development. Examples are: journalists, patients, members of ethics committees, venture capitalists, and politicians with a special interest in health, research, environmental, or industrial matters and others. In particular representatives from patient organisations should benefit from this knowledge to enable them to make a more strategic and considered input to medicines development. Furthermore, a greater in-depth understanding of the processes is needed for professionals more directly involved, e.g. SME personnel, project managers, general managers etc. A modular course to provide an overview of the medicines development process including regulatory, health economics and ethics requirements will be developed.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €3m.

18. Pharmacovigilance training programme

The science of pharmacovigilance is still developing from being traditionally reactive towards a more proactive focus on coordinating and analysing the wealth of data already available in the EU on the use of medicines. This change of focus requires inclusion of disciplines such as advanced epidemiology, biostatistics, drug utilisation, pharmacoepidemiology and use of large automated population-based exposure-

outcome databases. There is thus a pressing need to expand the knowledge of pharmacovigilance professionals in both industry and at regulatory agencies in order to support proactive pharmacovigilance and risk management of medicines throughout their life-cycle. An understanding of pharmacovigilance is also needed by e.g. journalists and patient organisations to improve their communication of hazards associated with medicines. Further, development of better methodologies for risk communication is needed. The project will achieve this by customised education and training programmes at three levels: short training courses for journalists, venture capitalists, patients, health care professionals, etc who require a basic understanding of the principles of contemporary pharmacovigilance; Masters level courses for professionals working within pharmaceutical companies and regulatory agencies; and long term programmes in benefit-risk communication.

Duration 5 years
Indicative total in-kind contribution from the EFPIA companies €3.5m.