IMI Call Topics 2008

Version of April 24, 2008

Table of Content

Introduction

The Innovative Medicines Initiative (IMI) aims to make Europe again the world leader in pharmaceutical research for the benefit of the economy and society, by removing research bottlenecks in the current drug development process.

The IMI Research Agenda has been developed through extensive consultation of all the relevant stakeholders. It describes specific recommendations organised around four areas:

1. Improving the Predictivity of Safety Evaluation: This addresses bottlenecks related to predictivity in safety evaluation and benefit–risk assessment;
2. Improving the Predictivity of Efficacy Evaluation: This addresses bottlenecks related to predictive pharmacology, the identification and validation of biomarkers, patient recruitment and benefit–risk assessment;
3. Closing the Gap in Knowledge Management: This addresses bottlenecks related to gaps in information technology, providing platforms to analyse large amounts of information in an integrated and predictive way. This pillar will be key to maximising the potential of new platform technologies such as genomics, and in analysing data generated by IMI in a consistently integrated manner;
4. Closing the Gap in Education and Training: This addresses the bottlenecks related to gaps in expertise in biomedical R&D knowledge and skills. This pillar will identify and address specific gaps in knowledge and capabilities. The education and training pillar will also ensure that Europe's biomedical education landscape is enhanced to provide maximum support in revolutionising the conventional drug discovery and development paradigm.

The IMI Call Topics for 2008 address three of these four pillars namely safety, efficacy and education & training. It is planned to start activities from the Knowledge Management platform in 2009.

This document describes the IMI Call Topics for 2008 to allow applicants to develop expressions of interests. The active participation of all relevant stakeholders and specially of patients organisations and regulators is critical to the success of IMI.

Appropriate consideration of existing initiatives/projects is to be made throughout the research to be performed, to benefit at the best achievable level from ongoing research in the pertinent field and to ensure complementarity between different initiatives/projects.

IMI Safety Pillar

The objectives of the research activities within the Safety pillar are to improve the predictivity of Safety evaluation during the research and development process. Under the first call in 2008, the activities will focus on immunogenicity, non-genotoxic carcinogenesis, in silico toxicity prediction, the discovery and qualification of safety biomarkers and the development of new pharmacovigilance methodologies. In addressing these topics, it is expected to improve attrition rates during early development and to strengthen the evidence base in pharmacovigilance.

1. Improve Predictivity of Immunogenicity

0	Topic Code	IMI_Call_2008_1_01
1	Topic title	Improve Predictivity and Minimization Strategies of Immunogenicity for Biotherapeutics in Man
2	Project description	**Background:** Immunogenicity is key to development of biotherapeutics, since it affects safety, efficacy and interpretation of study data. Need: Need to predict and minimize immunogenicity in man. **Issues:** 1. Limited comparability of immunogenicity data between assays 2. Factors or patterns favouring immunogenicity not well understood 3. Amount of data within individual companies too limited to verify predictive tools and minimization strategies 4. Lack of reliable prediction methods for immunogenicity and clinical consequences 5. Currently no possibility to stratify patients according to susceptibility to develop immunogenicity **Scope:** 1. Find ways to make immunogenicity analysis comparable between assays, compounds and companies 2. Gain big picture based on pooled relevant immunogenicity data 3. Investigate predictive value of pre-clinical tools (in-silico, in-vitro, animal models and stratification markers) 4. Share acquired knowledge Focusing on non-animal tools, refining existing animal models, gaining biomarker knowledge to stratify patients combined with potential to pool/share immunogenicity data

		amongst EFPIA and public consortia participants is well aligned to the 3R's principles (Refinement, Replacement, Reduction). The administrative and scientific core group of this project will be in contact with the EIP (European Immunogenicity Platform) co-chaired by Christian Ross Pederson (Novo Nordisk) and with the specialised groups of the American Association of Pharmaceutical Scientists (AAPS) to broaden the discussion with experts in the field and avoid redundancies. The proposal is to address these issues in three packages. **Package 1 (data comparability and big picture):** "Standardization" program for immunogenicity analyses: The assays available for immunogenicity analyses show significant inter-assay variability. Before evaluating predictive tool sets, which will be judged on predicting immunogenicity incidence in the clinic, it is crucial to make immunogenicity assay data comparable. Immunogenicity incidences are currently based on assay sensitivity and technology (affinity). For the different drug classes, international teams will conduct inter-assay, inter-laboratory, inter-company variability analyses. Data should be accessible via web-interfaces. Gain big picture: Long term program to improve the general understanding of the key factors leading to immunogenicity: Set-up of a database which is primarily fuelled by the companies of the consortium with immunogenicity relevant data from their biotherapeutic protein development programs. The database should improve the understanding of the predictive value of pre-clinical tools, help select and standardize the most promising predictive tool combinations for different compound classes, help evaluate and develop risk minimization strategies and re-evaluate and substantiate the "risk based approach to immunogenicity", outlined in the recently released EMEA guideline on Immunogenicity. Data mining will be applied to identify critical factors and patterns favouring the induction of immunogenicity in man. Validation of findings will be undertaken with new compounds. The database may contain the following aspects: • data on immunogenicity in pre-clinical animal models • data on in-silico and/or in-vitro risk assessment tools • humanization and/or de-immunization • cell-based versus soluble targets • HLA status of target populations • modes of administration

		• dosing regimens • immunogenicity data from clinical trials • drug properties (percentage of aggregates, proteolytic stability, etc) **Package 2 (predictive tools):** Improve tools to predict immunogenicity in man, based on at least 5 selected biotherapeutics (compare, verify, improve and validate existing tools, understand limitations and invite innovation). In-vitro: Perform side-by-side comparison of different versions of human APC/ T cell assays. Explore which of the assays, if any, is able to reliably reflect the immunogenic potential seen in clinical studies with respect to the overall immunogenicity incidence and HLA restriction of the responses seen with the respective drugs. Reference drugs are preferentially those that carry non-human sequences or artificial post-translation modifications. Improve throughput, reproducibility and thereby statistical relevance of data. Innovate existing assays where possible. In-silico: Subject selected biotherapeutics, which have displayed differential immunogenicity incidences in clinical trials, to in-silico screening for HLA-DR associated T cell epitopes by a set of established in-silico prediction algorithms. Consensus peptide agretopes from the results obtained by the use of several in-silico prediction tools, will be tested side-by-side in the most advanced APC/T cell assay (cf. package 2, above) together with the respective full-length biotherapeutics. This strategy will reveal which agretopes qualify as real T cell epitopes and will give rise to combinations of in-silico/ in-vitro tools with the highest predictive value. Innovate existing assays where possible. Animal models: Evaluate the predictive value of most promising animal models. • Analyse whether the transgenic mouse model that relies on breakage of tolerance, is dependent on T helper cells and MHC class II. In case yes, it is not a predictive tool due to MHC II species differences. • Analyse mouse models that rely either on human HLA-DR transgenes or human IgG genes or human hematopoietic stem cell transfer for potential to predict relative immunogenicity including formulation and manufacturing changes. • Evaluate utility of animal models to predict clinical consequences of immunogenicity (e.g. neutralisation of endogeneous counterpart, generation of super-agonist, target dependence of immunogenicity induction). Suitable compounds for the respective questions need

		to be chosen. • Evaluate utility of animal models to predict clinical consequences of immunogenicity (e.g. neutralization of endogenous counterpart, generation of super-agonist, target dependence of immunogenicity induction) • Reduce inter-animal variability which, as yet, is the major limitation of animal models. Stratification: Implement HLA typing as a standard tool in clinical studies and attempt to link immunogenicity incidence with the inherent risk of particular HLA-DR allotypes. If applicable, try to validate as stratification biomarker for potential to develop immunogenicity. **Package 3 (share acquired knowledge):** Draw conclusions from findings of package 1 & 2 and prepare recommendations on the most suitable tool package(s) for prediction and minimization of immunogenicity. Prediction: Recommend combinations of in-silico / in-vitro / in-vivo prediction tools that are tailor-made for individual compound classes such as: therapeutic antibodies, therapeutic proteins, new scaffolds, etc. Design a decision tree that takes into account different risk categories, dependent on indication, mode of administration, dosing scheme etc. Minimization: Inform about and recommend immunogenicity potential/risk minimization strategies based on identified key factors and patterns favouring the induction of immunogenicity in man (if applicable). Recommend for which compound classes (e.g. therapeutic proteins, antibodies) and in which situations (target, disease, etc.) de-immunization adds value and how this could be best achieved; in particular in those cases in which immunogenicity minimization is expected to give rise to decreased potency and in those cases in which there is a risk to induce auto-reactive responses in man unless the therapeutic protein is fully de-immunized. Reference drugs for in-silico and in-vitro systems are preferentially those that carry non-human sequences or artificial post-translation modifications, since these systems evaluate T-cell epitopes. In order to investigate animal models with respect to prediction of clinical consequences, appropriate compounds need to be chosen: e.g. compound with endogenous sequence for neutralization of endogenous counterpart. Standardization approaches should be evaluated for different compound classes.

3	Key deliverables of the project	**Package 1 (data comparability and big picture):** "Standardization" programme for immunogenicity assays: Drug class-specific standardization programme in order to improve comparability and quality of data defining immunogenicity positives vs. negatives. Database: Consortium-owned database that compiles immunogenicity relevant data including query tools. The database should be accessible via a web-interface allowing all consortium members to use a central on-line resource and to prepare a later publicly accessible database. The database should lead to an improved understanding of factors leading to immunogenicity, help re-evaluate and substantiate the "risk based approach to immunogenicity", outlined in the recently released EMEA guideline and support evaluation of existing predictive tools. **Package 2 (predictive tools):** Improved tools to predict immunogenicity in man, based on at least 5 selected compounds. In-vitro: 1-2 standardized, quantitative, high throughput (statistically relevant data generation) and clinically validated in-vitro APC / T cell activation assays (if applicable).These assays are to be compatible with formulated biologics and cover the 8-10 most frequent HLA-DR allotypes of the Caucasian population. In-silico: 1-2 standardized in-silico prediction algorithms that prove to be user-friendly and most reliable (in terms of false-positive promiscuous epitopes) when applied in combination with validated in-vitro models (if applicable). Animal models: Consolidated evaluation on the predictive value of different animal models for different types of aspects that are considered to contribute to immunogenicity. Stratification: HLA investigated as potential stratification biomarker for prediction of the individual risk of healthy subjects or patients to develop immunogenicity responses. **Package 3 (share acquired knowledge):** Recommendations for prediction and minimization of immunogenicity based on findings of packages 1 & 2. Prediction: Recommendation to apply combinations of in-silico, in-vitro and in-vivo tools which are tailor-made for mAbs versus non-mAb biologics and that account for risk differences in immunogenicity potential and clinical consequences. Differentiated recommendations will be summarized in focus reviews. Minimization: Consolidated recommendation for how to minimize immunogenicity potential/risk for different

		compound classes to be outlined in a focus review. Consolidated recommendation for whether and how to de-immunize therapeutic Abs versus recombinant non-Ab proteins that give rise to immunogenicity flags in pre-clinical assessment with the tool set described above.
4	EFPIA participants in the project	AstraZeneca, Bayer Healthcare, Boehringer-Ingelheim, Genzyme, Lundbeck, Merck, Merck Serono, Novartis, Novo Nordisk, Pfizer, Roche, UCB
5	Role of EFPIA participants in the project	Knowledge will be shared with the EIP expert group and with AAPS groups in the field (to synergize and align with existing initiatives and to avoid redundancies) and will be discussed with health authorities. Coordination by the consortium leader. Database: the EFPIA companies will provide relevant data for the database. Standardization: alignment with efforts by EIP including selected drug classes in order to make immunogenicity assay results comparable between assays, compounds and laboratories. Delivery of assays, assay data and generation of assay tools. Predictive tools: comparison, verification, improvement and validation of existing tools, understanding limitations and inviting innovation • In-vitro: Sharing existing assays with consortium members for collaborative evaluation and refinement. High-throughput format of selected assay will be implemented by industry, if applicable. • In-silico: Sharing existing tools with consortium members. Comparing and improving existing algorithms: Testing in industry application. • Animal models: Sharing existing animal models with consortium members for collaborative evaluation and refinement. Testing relevant animal models provided by public sector in industry application.
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 13 million Package 1: € 3 million Package 2: € 8 million Package 3: € 2 million
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The Applicant Consortium is expected to address all three packages. The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Scientific input for innovative approaches to further elaborate assays and animal models.

		• Database: Setting up of database and data mining. • Standardization: Elaboration and validation of standardization approach. Sharing existing assays, data and assay tools. • In-vitro: Investigating the potential of in-vitro models to predict immunogenicity. Sharing existing tools with consortium members. Sharing novel insights into relevant areas of science (e.g. relevant components of system, limitations, innovative approaches). • In-silico: Sharing existing tools with consortium members. Providing intellectual input to compare, evaluate and improve the predictive value of currently existing algorithms. • Animals models: Investigating the potential of animal models to predict immunogenicity and/or clinical consequences. Sharing relevant animal models to be tested by industry and novel insights into relevant areas of science (e.g. comparability of immune systems between species).
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 9.0 million for this project.

2. Non-genotoxic Carcinogenesis

0	Topic Code	IMI_Call_2008_1_02
1	Topic title	Non-genotoxic carcinogenesis: Identification of early markers and molecular classification of tumours
2	Project description	**Background:** 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. Furthermore, by the time the rodent bioassay is complete, hundreds or even thousands of patients may have been treated in a clinical development program. The applicability of early biomarkers in the assessment of non-genotoxic carcinogenesis in preclinical rodent toxicity studies has thus far not been conclusively established. Even in those cases where candidate biomarkers have been suggested for specific carcinogenic effects, it is unknown whether the biomarkers involved are mechanistically or causally involved in cancer development. Thus, 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. A major long-term benefit of validating robust, early biomarkers of non-genotoxic carcinogenesis is the reduction in the number of animals used for cancer bioassays. This project consists of an initial 2-year “Exploratory Phase” during which the focus will be on evaluating the utility of new experimental models and tools for investigating the following emerging areas of science relevant to non-genotoxic carcinogenesis: **(1) Epigenetic mechanisms of carcinogenesis** Recent investigations indicate that epigenomic alterations (e.g. altered DNA methylation status and/or histone modifications) may precede the expansion of pre-malignant cells during the earliest stages of tumourigenesis. Thus, epigenomic profiling represents a powerful approach for evaluating mechanisms of toxicity and biomarker identification. In particular, this approach would complement and build upon existing mechanistic and predictive toxicogenomic studies in which a range of genotoxic and non-genotoxic carcinogens have already been profiled. Together,

		a combined genomic/epigenomic profiling approach should contribute to the assessment of human cancer risk at a much earlier point in the pharmaceutical development process. **(2) Receptor-mediated mechanisms of carcinogenesis** In vivo carcinogenic effects often depend upon drug-receptor interactions. For example, PPARα and CAR agonists induce liver tumours in rodents through mechanisms that are not fully elucidated, but require the presence of receptor proteins. A number of transgenic mouse models (knock-in, knock-out, humanised) could be exploited to assess the role of nuclear receptors in drug-induced carcinogenesis. Early biomarkers or surrogate endpoints for receptor-mediated carcinogenic effects may be immensely valuable for increasing speed and reducing volume in preclinical development, as well as to facilitate bridging from preclinical studies to human trials. **(3) Molecular classification of tumours** The intrinsic chemical stability of DNA in both frozen and fixed tissue samples represents a unique opportunity for the application of epigenomic and other molecular profiling technologies to "unlock" the extensive preclinical tissue archives generated from carcinogenicity testing within the pharmaceutical industry. The molecular classification of spontaneous versus chemically-induced tumours may be accomplished via combined epigenomic and gene expression profiling of archived rodent tissues from these long-term carcinogenicity studies. Important outputs of such efforts include collation of baseline molecular signatures from spontaneously occurring tumours in aged animals, and the identification of biomarkers which may be applied to the early assessment of non-genotoxic carcinogens. **(4) Circulating tumour cells/nucleic acids** The presence of tumour-specific circulating cells, nucleic acids and methylated DNA in plasma or serum represent promising biomarkers for the early detection of cancer. The conceptual and technical feasibility of identifying circulating tumour cells in preclinical rodent models has not yet been explored. In addition, the predictive value of tumour-specific circulating nucleic acids and/or methylated DNA in plasma or serum as non-specific surrogate biomarkers of non-genotoxic carcinogenesis should be assessed in preclinical studies. **(5) Protein markers / in vivo imaging** It is well-recognized that neoplastic transformation is associated with changes in intracellular signalling cascades (e.g. protein phosphorylation), as well as changes in transcription factor expression. Accordingly, in some model systems of receptor-mediated carcinogenesis, early protein phosphorylation and transcription factor expression changes may represent biomarkers of carcinogenicity. Recently developed mass-spectrometry-based methods appear quite promising as biomarker identification tools, allowing a

		Systems Biology approach to the study of complete phospho-proteomes of cells. Multi-labelling histopathological approaches, with the potential to localize and quantify a carcinogen receptor as well as a biomarker in relation to pre-neoplastic lesions, will be useful for evaluating mechanisms and causal effects in cancer development. Finally, in vivo imaging of early pre-neoplastic lesions in experimental animals constitutes a highly promising approach to shortening carcinogenicity study duration, increasing study power, and reducing the number of experimental animals. **Impact of the Project:** The applicability of early biomarkers in the prediction of non-genotoxic carcinogenesis in preclinical rodent toxicity studies has thus far not been conclusively established for small molecule compounds, and has essentially not been addressed at all for protein/peptide compounds. The main impact of the project will thus be to establish, for the first time, proof of concept that early biomarkers can reliably and robustly predict later cancer development. Early biomarkers of carcinogenicity would be immensely valuable in preclinical development of new compounds, allowing reduction/refinement/replacement of experimental animal use, improved internal selection of super-qualifier compounds, fewer delays and attritions during late-phase development, and improved preclinical carcinogenicity safety assessment prior to clinical trials. Translation of early cancer biomarkers into the clinic would also improve safety for Phase III patients. The development of standardized software tools and procedures is essential for use by pharmaceutical companies and Regulatory Authorities for preclinical safety, human risk assessment, and regulatory decision-making. A collaborative pan-European approach will facilitate access to a wide range of archived tissue resources and molecular profiling databases and also generate a robust framework for ultimate qualification of newly identified early biomarkers for non-genotoxic carcinogens. Pooling and sharing of existing archived animal tissue samples for the studies outlined in this call would be well aligned to the 3R's principle of reduction, refinement & replacement through maximizing the knowledge gained from extensive preclinical carcinogenicity testing programs. Furthermore, the establishment of blood-based surrogate biomarkers such as methylated DNA should ultimately lead to the use of fewer animals in carcinogenicity studies through serial sampling regimes. This topic is linked in a synergistic manner to the IMI topic "Development of expert (QSAR) systems for in silico toxicity prediction" (page 17) which explores in silico prediction of chemical structures linked to early biomarkers found to predict tumourigenesis.

3	Key deliverables of the project	1. Identify industry-relevant model systems, using small-molecule and biopharmaceuticals, for mechanistic studies of epigenetic and/or receptor-mediated non-genotoxic carcinogenic effects, including biomarker identification. 2. Investigate predictive value of novel early mechanism-based biomarkers across diverse classes of non-genotoxic carcinogens in preclinical animal models. 3. Explore utility of circulating tumour cells and methylated DNA as blood-based surrogate biomarkers for non-genotoxic carcinogenesis 4. Compare biomarker findings between preclinical animal models and humans to investigate the potential and robustness of such biomarkers for translation into the clinic. 5. Generate a unique database of molecular profiles of spontaneous and drug-induced rodent tumours.
4	EFPIA participants in the project	Bayer Healthcare, Boehringer-Ingelheim, Lundbeck, Novartis, Novo Nordisk, Pfizer, Solvay, UCB
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Tissue and blood samples from long-term rodent carcinogenicity studies. • Tissue and blood samples from short-term mechanistic studies. • Evaluation of samples using genome-wide and locus-specific epigenomic profiling technologies including DNA methylation and histone modifications (staff; laboratories; cost of reagents and materials). • Evaluation of samples using genome-wide and locus-specific gene expression technologies including Affymetrix microarray and quantitative real-time PCR (staff; laboratories; cost of reagents and materials). • Evaluation of samples using molecular pathology tools and assays (e.g. Laser-capture microdissection) for assessing cell-type specific molecular responses to non-genotoxic carcinogens. • Development and application of bioinformatic tools for combining epigenomic and genomic profiling data. • Evaluation of samples using classical immunohistochemistry and in situ hybridization approaches, to correlate carcinogen receptor as well as biomarker expression to sites of tumour formation. • Evaluation of potential for translation of preclinical biomarkers to the clinic. • Receptor binding studies comparing carcinogenic and non-carcinogenic ligand versions. • Phosphoproteome analysis of animal and human cell

		cultures exposed to model carcinogens. • Specific examples of relevant “in-kind” contributions to this call could include the costs of running carcinogenesis and associated mechanistic studies, provision of existing archived samples from such studies, development of technologies in support of epigenomic profiling assays, development of bioinformatic tools for integration of epigenomic and genomic datasets.
6	Indicative duration of the project	2 years (Exploratory Phase) 3 years (Confirmatory Phase) We envisage a 2 year exploratory phase in which one or more emerging innovative experimental models and/or technologies outlined under the “Project description” in section 2 will be evaluated for their utility to provide mechanistic insights and candidate biomarkers for nongenotoxic carcinogenesis in rodents. Peer review of results from the initial 2 year Exploratory Phase would be a milestone at which a decision would be taken on whether to trigger continued funding for an additional 3 year Confirmatory Phase. The Confirmatory Phase will involve validation of carcinogenic mode of action hypotheses and early carcinogenesis biomarkers by optimized biomarker assays (more stringent validation criteria, higher throughput), broader tissue sample access, and a larger panel of test and reference compounds. Additionally, the 3 year Confirmatory phase would focus on investigating the mechanistic involvement of early biomarkers in later cancer development, i.e., cause-effect relationships. Finally, in the 3 year Confirmatory phase, clinical translation of selected rodent carcinogenesis biomarkers may be undertaken. Importantly, combining both Exploratory and Confirmatory phases in a single IMI call, maximizes the chance of biomarkers identified during the exploratory phase being put to actual practical use. In addition, the 2 year Exploratory Phase milestone and associated peer review process presents a high degree of scientific challenge, thereby maximizing the chance of attracting innovative Applicant Consortium partners. Finally, the technological and sampling strategies selected for biomarker identification in rodents can have profound implications for later biomarker assay validation, throughput optimization, and clinical translation. During both the Exploratory and Confirmatory Phases, major benefits of this IMI call would be to 1) maximise mechanistic/biomarker knowledge gained from preclinical carcinogenicity testing programs and to 2) facilitate access to a broad range of archived rodent tissues amongst EFPIA and public consortia participants. These benefits are expected to improve our ability to evaluate the human relevance of nongenotoxic carcinogenesis findings in rodents, which currently constitutes a significant bottleneck in drug development. Furthermore, both these benefits are well aligned to the 3R’s principles (Refinement, Replacement, Reduction).

7	Indicative total in kind contribution from the EFPIA companies	€ 2.5 million (Exploratory Phase) € 10 million (Confirmatory Phase)
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Establish industry-relevant animal models for mechanistic studies of epigenetic and/or receptor-mediated carcinogenesis. • Develop innovative molecular technologies/assays for identification of candidate early cancer biomarkers in animal tissues and blood samples. • Develop innovative molecular technologies/assays for molecular classification of rodent tumours. • Integrate experimental biomarker data with molecular profiling data from public domain (e.g. CEBS, Human Epigenome Project), commercial (e.g. Iconix) and EFPIA consortia molecular profiling databases. • Evaluate validity of candidate biomarkers using well characterised preclinical animal models and drugs associated with nongenotoxic carcinogenesis. • Explore the predictive nature of early biomarkers. It is recognised that this item may not be fully addressable within the duration of the call, due to complexity and cost of performing long-term animal studies. This goal would most likely be achieved during a second “Confirmatory Phase” of the project following a successful outcome of the initial 2-year “ Exploratory Phase”. • Clinical translation of selected early rodent carcinogenesis biomarkers, including potential use of cell-based (e.g. human hepatocytes) and/or “humanised” animal models. This goal would most likely be achieved during a second “Confirmatory Phase” of the project following a successful outcome of the initial 2-year “ Exploratory Phase”.
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 9.0 million for this project.

3. Expert Systems for in silico Toxicity Prediction

0	Topic Code	IMI_Call_2008_1_03
1	Topic title	Development of expert (QSAR) systems for in silico toxicity prediction
2	Project description	**Background:** In vivo studies are often unveiling 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. This would also reduce the number of animals (3Rs) used in preclinical studies necessary to select drug candidates. **Approaches:** 1. Collect pharmacology-related chemistry ("molecule war-heads") from known series to build up predictive expert systems for secondary pharmacology ("off-target toxicity") prediction. 2. Same approach as above for pure chemistry-related toxicity (e.g., cationic amphiphilic drugs and phospholipidosis). 3. Exploit legacy preclinical reports from the pharmaceutical industry to link chemical features to pathology findings and extract patterns for in silico prediction. The individual steps to be taken for the development of expert/QSAR systems comprise: • Identification of different database scenarios (restricted access, limited sharing or full sharing) for data sharing to overcome obstacles which may exist (IP protection). Necessary contractual frameworks will be established for the different scenarios. The collection of proprietary data and the database administration may alternatively be centrally undertaken by an external partner. The database will be assembled on the basis of public and shared mammalian repeat dose toxicity studies (mainly legacy report data). Synergies with PredTox I and II (already existing database structure, harmonized vocabulary for histopathological findings in liver & kidney and database content) will accelerate this step. • Collection of study data and associated information (including treatment and sampling schedules) and of experimentally measured observations on samples. Sample data include phenotypic anchors and omics data (including transcript, protein and metabolite

		profiles). • Pre-processing of experimental raw data and storage in relation to their corresponding experimental samples (including reliable data quality assessment of large amounts of molecular data from all omics technologies). • Establishment of relationships for experimental data (including cross-omics mappings, mappings of different platforms within a given omics technology, and mappings of legacy data with current data to extract maximum value from existing corporate knowledge). • Comprehensive statistical analysis and determination of discriminating markers (using sophisticated feature selection tools) for potential toxic effects. • Application of modeling approaches such as support vector machines, K-nearest neighbour, decision trees, Gaussian processes, to predict compound toxicity and compound mode of action. • Interpretation and validation of markers in biological context (e.g. specific pathways). • Reliable documentation of markers to support informed decisions on promotion, termination, or re-evaluation of compounds, based on their comprehensive toxicological signatures. This project will initially concentrate on a common ontology of histopathology descriptions and extraction of toxicology findings from legacy toxicology reports. In parallel, solutions for overcoming sensitive data sharing issues will be worked out. Then, modelling of these findings will constitute the second phase of this consortium. It is recognised that the data collection phase might be long due to the complexity and heterogeneity of pharma reports. Hence, it is hard to predict the length of the initial phase. However, academic partners should be already involved for working out solutions for data sharing and ontology issues. **Requirements:** Software In order to predict potential off-target interactions, the following will be necessary: expert/QSAR systems (e.g., Mcase, DEREK, etc), pharmaco-toxicological databases with chemical structures and associated pharmacology/toxicity populated with data from both public domain and pharmaceutical companies, access to MDS Pharma-like in vitro receptor binding assay results. Usage and implementation will only require personal computers and experts for running, maintaining and regularly updating the systems.

		Knowledge Management The requirements mainly depend on the data being captured. Due to the 5 year time frame, an “off the shelf” solution for a database is recommended. Potential partners should allow the gathering of all relevant information including adaptation of the database structure, vocabularies, report conversion and population and maintenance of the database. Project Management For Project Management and data sharing there are a number of web-based tools that can be supported within a company or externally. The objective is to allow project management (timelines/task management), document sharing, discussion forums, automatic communication by email etc. Cheminformatics Existing data from known toxicities will be fed into databases and used further to develop knowledge expert and QSAR systems for prediction of in vivo toxicity. For model development, we would have to either include many, i.e. >>100s of compounds that are structurally very different but give similar toxic endpoints, or we would need to focus on compounds having similar scaffolds but very different levels of toxicity in order to create algorithms to improve the prediction of toxicity based on chemical structure. In detail, models will be set up for the subset of predictable categories (e.g. defined target organ, histopathological endpoint, or molecular target) applying various molecular descriptors and new statistical tools to model development. Various approaches, including 3D-QSAR for receptor-mediated effects and so-called feature selection tools, as well as other sophisticated algorithms will be pursued. The most appropriate modelling approach(es) will then be selected based on predefined criteria. Furthermore, the combination of models predicting ADME and toxicology properties in a single model to achieve the prediction of the primary target organ(s) will be evaluated. The developed models will be delivered to the consortium members for analysis and evaluation. An additional approach will be the establishment of cross-linkage to further projects within IMI by correlating structures to omics endpoints (e.g. metabonomics). A link could be established to the “Non-genotoxic carcinogenesis” project in order to establish correlations between tumourigenesis biomarkers and structural or molecular features for in silico prediction. Alternatively, meta-tools (i.e. tools which can be trained individually by each user) will be developed to be used in the companies for in-house modelling to circumvent legal

		hurdles in data sharing. Bioinformatics We will need software for identifying the human orthologues of biomarkers identified in animal studies in order to translate the findings in pre-clinical omics studies to clinical omics studies. Much of this is open source (BLAST etc.) but will perhaps need development and support.
3	Key deliverables of the project	• A toxicological database with high quality in vivo data (e.g. from systemic toxicity studies) and secondary pharmacology in vitro assays. This repository will form the basis of prediction model development. • Critical assessment of the diverse approaches towards in silico toxicology and their value in drug discovery and development. • Construction of prediction models for selected in vivo endpoints to identify compound liability for target organ toxicity and to identify the primary sensitive target organ(s) after systemic exposure, with a possible additional link to the “non-genotoxic carcinogenesis” project. • A successful outcome will initiate the validation of these prediction models on the basis of the proposed OECD principles. The validation experience will be shared between companies and with regulators.
4	EFPIA participants in the project	AstraZeneca, Bayer Healthcare, Boehringer-Ingelheim, Esteve, GSK, Lundbeck, Novartis, Pfizer, Roche, UCB
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Identification of critical issues in data sharing • Definition of endpoints, parameters and variables essential for database setup and model development. Identification of synergies concerning database structure and setup. • Retrieval of legacy data from archives (paperwork or electronic repositories), conversion into electronic file format (*.pdf or other suitable electronic format), if applicable. • Shipping of pre-processed legacy data to external partners for conversion into database-importable format. • Quality check of converted data and submission to external partner for population of database. • Evaluation of prediction models (toxicological expertise) developed by the Applicant Consortium. • Guidance for validation exercise by establishing interface between the Applicant Consortium and regulatory authorities.

6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 5 million
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Technical approaches to circumvent obstacles for data sharing, development of software tools for coding/decoding sensitive data. • Preparation and curation of data sets for model development. Statistical analysis of endpoints amenable to modelling. • Proposals for harmonization of histopathology ontology terms for in vivo findings. • Provision of meta-tools (i.e. tools which can be trained individually by each user) to participating companies. • Applications of feature selection tools and sophisticated algorithms for QSAR model development. • Validation and documentation of models meeting the needs described in the OECD principles for Expert systems/QSAR validation.
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 4.0 million for this project.

4. Improved Predictivity of non-clinical Safety Evaluation

0	Topic Code	IMI_Call_2008_1_04
1	Topic title	Improved Predictivity of Non-Clinical Safety Evaluation
2	Project description	The goals of this project are to assess the value of combining results from 'omics technologies together with the results from conventional toxicology methods for a more informed decision making earlier in preclinical safety evaluation. The intended project aims to focus on the combined application of well-known toxicological endpoints (histopathology and clinical chemistry) and novel technologies (toxicogenomics, metabonomics and proteomics) to evaluate hepatotoxicity and nephrotoxicity. For this purpose, proprietary and reference substances will be selected as test compounds. During the first phase of the project, in-vivo studies in rats will performed using a harmonized experimental protocol. Conventional toxicology end points and 'omics data will be collected and evaluated. Data will be submitted and stored in an appropriately designed database. The generated data will be analyzed in depth within and across platforms and across studies and mechanisms of toxicity, aiming towards a systems toxicology approach. The underlying molecular mechanisms of toxicity will be investigated. The generated mechanistic hypotheses will be followed up with suitable experiments. In this context, identification and qualification (for non-clinical purposes / use only) of novel biomarkers for selected toxicities across relevant species is proposed. These safety biomarkers will be used early in preclinical development of new drug candidates for selection and characterisation in order to focus on development of promising medicines. The relevance of this approach is closely linked to acceptance of new biomarkers by Regulatory Authorities. Therefore, critical review together with Regulatory Authorities is of key importance. The final goal is to integrate new, qualified methods into non-clinical safety assessment. The envisaged research program 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 ~10-15 well characterized drug candidates from participating companies and ~10-15 reference compounds. The compounds will be selected based on toxicity findings in the liver and/or kidney and the discovery of biomarkers

		for regulatory decision making will be based on cross-'omics comparison as a major part of the evaluations. The research activities must focus on: • Bioinformatics: Improved biostatistical models and novel approaches of data integration with strong emphasis on biological interpretation. • Mechanistic Investigations: The generated biological hypotheses need to be thoroughly assessed and new technologies may be used to confirm or reject these hypotheses (e.g. additional assays, in vitro systems, etc). • Development of tools, technologies, assays, standards, and procedures that can be used by pharmaceutical companies for application in standard toxicity studies, and potentially, for regulatory decision making. • Essential part of the activities has to be the co-operation with other consortia focusing on non-clinical safety (e.g. C-Path – Preclinical Safety Testing Consortium, Health and Environmental Sciences Institute- HESI) and with the corresponding IMI programme on translational biomarkers which investigates biomarkers for human use in the clinical setting. The project will set the framework for generating data and interchanging knowledge across companies and universities. New (innovative) methods and approaches from Universities, Small- and Mid-size Enterprises and other potential partners should be integrated. Potential public participants can take advantage of the availability of advanced technical capacities and capabilities of applied research of industry and of an efficient project management. One essential driving factor for the project is the intention to contribute to the 3R's (Refinement, Reduction, Replacement). Refinement: Application of latest technologies and methods in combination with an intelligent study design will improve the relevance of animal studies, especially with regard to extrapolation of non-clinical safety data to humans. Reduction: All experiments will be executed using latest state-of-the-art procedures at the lowest animal numbers needed to provide relevant results. As new technologies may offer higher sensitivity, incorporation of these tests in preclinical testing may reduce the number of animals in future studies. In addition, higher sensitivity should allow the detection of toxicity at lower doses and/or after a shorter exposure time, therefore reducing the animal stress.

		Replacement: Under a short – or mid-term perspective it is less likely that a replacement can be claimed based on the potential results of this research proposal, but it may be possible to identify one relevant species for preclinical testing of specific compounds, rather than using two (rodent and non-rodent) by default.
3	Key deliverables of the project	• A valid, relational, high quality database for improved predictivity of safety evaluations. • The database should enable the detection and characterization of specific biomarkers of safety. Increased number of relevant compounds, quality of data, integration of data, and prediction models should also facilitate mechanistic investigations. • Novel non-clinical biomarkers for hepato- and nephrotoxicity will be identified, which can be used for cross-species investigations; understanding the biological mechanisms underlying the observed toxicity for the derived biomarkers. • The identified biomarkers will be qualified for use in non-clinical safety assessment through assay development and characterization. • A generic process for qualification / validation of biomarkers for use in non-clinical safety assessment will be established and discussed with regulatory authorities. • The relevance of identified biomarkers for non-clinical safety testing in this project will be assessed together with Regulatory Authorities. • A communication / dissemination strategy will be implemented. A training programme in understanding / practising of the methods used and biomarkers identified will assure that there are more specifically-educated scientists available.
4	EFPIA participants in the project	Bayer Healthcare, Boehringer-Ingelheim, Merck Serono, Novartis, Orion Pharma, Roche, Sanofi Aventis, Servier, Solvay, UCB
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • to the development of all study protocols for in vivo studies and laboratory investigations. • animal experiments, mainly in rats will be performed by EFPIA participants with special analyses (clinical chemistry, histopathology, etc.). • studies in non-rodents using new approaches (adaptive trials involving biopsies) if necessary. • investigation and evaluation of samples for transcriptomics, proteomics and metabonomics (laboratory; staff; costs of reagents, microarrays). • development and evaluation of new assays and

		techniques such as immunoassays, immunohisto-chemistry (IHC), in-situ-hybridization (ISH), laser-capture micro-dissection, as deemed necessary. • project management as related to the research activities.
6	Indicative duration of the project	3 years
7	Indicative total in kind contribution from the EFPIA companies	€ 10 million
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Histopathological evaluation, tissue microarrays, digital slide scanning and automated image analysis. • Transcriptomics technologies are necessary to supplement lacking capacities in industry. • Latest methodologies, e.g. quantitative mass spectrometry: LC/MS & GC/MS and 1H-NMR techniques are needed to allow for highest standards in the field metabonomics. • Capabilities in proteomic profiling via SELDI, 2D-DIGE, iTRAQ etc analysis are necessary. • In order to comply with the request of mechanistic and confirmatory studies, relevant public capacities and capabilities are needed. This includes assay development, i.e. using quantitative RT-PCR and in-situ hybridization. • Hosting and maintenance of the necessary database infrastructure has to be provided. This includes the availability of infrastructure and services for centralized assessment and processing of all data and construction of a project-related database. • Capabilities in development of approaches and infrastructure for integrated data analysis, including building of biostatistical models based on all experimental data are necessary. • The expertise in biological interpretation / integration of results can only partly be provided by industry and contribution from external experts appears to be highly essential. • The Applicant Consortium should include representatives from the Regulatory Authorities because the relevance / utility of identified biomarkers for non-clinical safety testing is heavily dependent on acceptance by the authorities granting drug approvals and in charge of taking care for public health / safety.

9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 7.0 million for this project.

5. Qualification of Translational Safety Biomarkers

0	Topic Code	IMI_Call_2008_1_05
1	Topic title	Qualification of Translational Safety Biomarkers from Non Clinical to Early Clinical Studies
2	Project description	**Background:** 1. A lack of specific and sensitive mechanistic safety markers and their respective assay for human samples is regularly delaying drug development programs. This is especially the case when a histo-pathological signal is seen in preclinical toxicology studies which cannot be adequately monitored in humans. 2. Furthermore, the predictivity between non-clinical and early clinical studies of currently accepted markers is very poor (e.g. for drug induced vascular injury no translational biomarker is qualified, or markers of fibrosis in different organs are either still only exploratory or have been only used pre-clinically). 3. 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. 4. 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 (FP6 PredTox, PSTC, ILSI/HESI) 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 and also in consultation with other groups like the Preclinical Safety Testing Consortium to avoid redundancy and to exploit complementarities. **Background on Drug Induced Liver Injury (DILI):** The predictability, mechanistic understanding and monitoring for DILI in preclinical and clinical settings are not specific or sensitive enough to distinguish DILI from other causes of liver injury or from adaptive responses to drugs. The biomarkers used now in man and animal species are relatively good at detecting gross hepatocyte dysfunction or cell integrity but are not sensitive or specific enough to distinguish early DILI from other causes of derangement in liver biochemistry or from adaptive hepatic responses, nor

		can they predict which subjects will recover from those who will go on to develop fulminant liver disease. There is a big need to develop new biomarkers for DILI and also to understand more about predisposing factors for DILI (both genetic and environmental). We also know that many mechanisms triggering DILI cannot be mimicked in preclinical studies and a single validation exercise for biomarker candidates from preclinical projects would exclude potentially important biomarker candidates obtained by back-translation from human samples. A key to the solution of this problem lies in obtaining good quality clinical material from individuals experiencing DILI, as well as from individuals suffering from non-drug related liver injury. **Background on Drug Induced Kidney Injury (DIKI):** DIKI is not an uncommon adverse event in drug development and is affecting various classes of drugs, e.g. in the field of oncology, immune suppression, or antibiotics. Looking at the anatomy and function of the kidney, it is straightforward to understand why. The kidney is basolaterally exposed to xenobiotics circulating in blood but also luminally exposed to these entities, which are filtered and concentrated in the kidney. In many circumstances DIKI and especially its acute form could be prevented or at least minimized by screening and monitoring with appropriate tools and early intervention. At this time, the main problem is the late identification of acute kidney injury linked to the current standards, i.e. serum creatinine (sCr) and blood urea nitrogen (BUN). These are late indicators of renal injury, which might not be significantly changed until 2/3 of the nephron function has already been lost. During recent years a number of urinary biomarkers have emerged to monitor the integrity of the kidney rather than its function like sCr and BUN, but they almost all lack clinical validation to be useful for regulatory decision making. **Background on Drug Induced Vascular Injury (DIVI):** When DIVI is detected through histo-pathology in preclinical toxicology studies, compounds are most often put on hold since there are no adequate biomarkers to monitor this pathology in Phase I and II human safety trials. DIVI can involve altered haemodynamic forces (shear stress) on the arterial wall, direct drug induced toxicity or immune-mediated injury of endothelium (± medial smooth muscle). Historically the majority of DIVI in humans is pathogenetically inflammatory in nature, affecting small arterioles and venules and generally an immune-mediated process is suspected. In preclinical species, endothelial compromise appears as an early event. Drugs that cause altered vasoreactivity (constriction, dilation) administered either acutely or chronically may be factors in lesion induction and remodeling that influence chronic vascular injury. Current biomarkers of vascular injury in humans are

		non specific and of limited sensitivity (e.g. CRP, ESR, ANCA, immune complexes). **Project plan:** Qualification Process: Define different options for a potential generic process for clinical validation of translational safety biomarkers (BM) and discuss with Health Authorities to check acceptance and the key elements to be focused on during the test period: • current standards/ parameters used in clinical situation to define/monitor the need for treatment or treatment change. • applicable parameters for identifying the population to treat/monitor. • control ranges applicable to these parameters and the out of range limits for which the treatment/BM application scheme would be applied. • whether recovery (i.e. normalization of the parameters to control range) is anticipated and if not, what are the acceptable range values of a BM for an effective maintenance or change of treatment. • a scheme for assessing the clinical utility/value as opposed to current standards. • possible interfering situations/parameters which would influence the control range or the treatment range for each BM or for a combination of BM. • selection of mechanistic biomarkers from different non-clinical discovery or qualification exercises (e.g. FP6 PredTox, C-Path PSTC, etc) based on their potential for translational use. • establishment of assays and sampling protocols in human to provide enough diversity of pathological responses to qualify the biomarkers for these responses versus clinical endpoints and with respect to current standards. (analytical and biological validation). • baseline human trial studies to understand variability and define control values and the appropriate control ranges for the different populations under investigation (e.g. healthy subjects and different types of patient). • selection of a subset of related diseases or drugs (based on basic mechanistic understandings) which could influence the biomarker profiles and mislead interpretation (i.e. tests of specificity). DILI specific project plan: Select mechanistic biomarkers for DILI from different non-clinical discovery or qualification exercises for clinical validation. Examples would include markers from: • FP6 PredTox (no candidate biomarkers yet)

		• PSTC (MDH, GLDH, PNP, PON-1,) DIKI specific project plan: The new markers cover the integrity of different compartments such as proximal tubules (KIM-1, GST-α, Lipocalin-2) or distal tubules (GST-π) but also different molecular events such as the integrity of the glomerular filtration barrier (Total Protein, Albumin, Clusterin), tubular re-absorption processes (Cystatin C, β2-Microglobulin), regeneration processes (KIM-1), and cell leakage (GST-α, GST-π). A number of these markers are currently being qualified for regulatory decision making in pre-clinical settings by the C-Path Predictive Safety Testing Consortium (PSTC) together with the regulatory authorities EMEA and FDA. Clinical qualification will include assessing control ranges, thresholds, sensitivity and specificity for different patient populations and pathologies. DIVI specific project plan: Mechanistic biomarkers for DIVI will be selected from different non-clinical and clinical discovery or qualification exercises such as those from PSTC, ABPI and others. Clinical translation of preclinical assays will be explored in early clinical trials.
3	Key deliverables of the project	What the project aims to achieve after completion: 1. A generic process of clinical validation of translational safety biomarkers. 2. The clinical utility/use of the biomarkers selected for qualification and judgement on the benefit provided. 3. A set of biomarkers for drug induced injuries, and their assays, both qualified for use in early safety clinical trials. Definition of control ranges and cut-off values for different populations and different clinical utilities. 4. Assays and their performances. Also identification of potential partners willing to develop and produce the assays. 5. A basic understanding how patient specific factors (e.g. diseases, other drugs,…) can influence the biomarkers. 6. A database of human biomarker profiles with a detailed characterization of clinical, individual and drug-specific factors in the context of drug-induced toxicities and diseases. 7. A communication/training plan and identification of the target audience to implement effectively the results and including monitoring plans to assess successful implementation. 8. A biobank of the material collected for clinical validation of biomarker candidates would also be highly suitable for novel biomarker discovery for DILI, DIKI and DIVI, with particular emphasis on biomarkers of predisposition and organ changes in the triggering, progression and resolution phases, utilising genetic, proteomic and metabonomic analysis platforms. This

		project could provide a unique biobank for biomarker discovery if samples can be made available to study human-specific biomarkers.
4	EFPIA participants in the project	Almirall, Amgen, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, GSK, Johnson & Johnson, Merck Serono, Novartis, Pfizer, Roche, Solvay
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: Options for a qualification process: Such a process once made official and taken up by Health Authorities would facilitate the emergence of new qualified biomarkers largely beyond the scope of this call. Markers having sufficient pre-validation data to give them a high probability of becoming “validatable”. Such markers would improve the predictivity of non-clinical safety studies and have a positive impact on attrition rates and drug development timelines. They will also possibly allow the reduction of animal trials by moving compounds faster to clinical phases. Some companies of EFPIA are already using some of these biomarkers pre-clinically or clinically although not for regulatory purposes. Examples of DILI and DIKI markers for which EFPIA members could contribute data and experience: • DILI: Cytokeratin 18 [M35 for apoptosis/M60 for necrosis] as structural marker, liver-specific coagulation factors such as PT as functional markers, cytokines [pro- and anti-inflammatory], LECT-2 [an NKT cell chemokine specific for the liver], calpain and calpain-specific matrix protein fragments, ALT1/ALT2 isoforms,… • DIKI: all potential candidates, for which EFPIA members have already pre-clinical data, such as Kim-1, Albumin, Total Protein, B2Mic, NAG, Clusterin, Urinary Cystatin C, Plasma Cystatin C, TFF3, GST-α, GST-π, Lipocalin-2, Timp-1, Osteopontin, IL-18, RBP. In clinical settings several markers have already been used to diagnose kidney diseases (Total Protein, Kim-1), to monitor allograft rejection (GST-α, GST-π), ischemia (Lipocalin-2, Kim-1) or drug-induced nephrotoxicity (Kim-1, GST-α, NAG). Yet, a systematic qualification of these markers in a clinical setting is still lacking, rendering these markers unusable for regulatory decision making. Clinical trials and samples: The EFPIA members will collect extra samples from current clinical trials such as: • Additional blood/plasma or urine samples from Phase I healthy subject trials and Phase II safety studies in patients. These samples could be further analyzed to define the variability ranges and the sensitivity of the new markers. • Additional blood/plasma or urine samples from studies

		in populations with different types of disease during Phase III and Phase IV trials. Samples from diabetes patients would for example be extremely helpful to study the specificity of new biomarkers. The same would apply to samples from obese patients or from patients with cardiovascular diseases for any of the studied injuries DILI, DIKI or DIVI. Furthermore, companies are regularly conducting regulatory pharmacokinetics or safety studies in impaired kidney and liver patients. Additional blood/plasma or urine samples from these kind of studies would also be extremely useful for this qualification process and will be contributed by EFPIA companies. EFPIA contributors will consider sponsoring, designing and conducting a limited number of clinical studies specifically dedicated to answering a particular sensitivity or specificity aspect of the qualification. Biomarker assays: For some biomarkers, EFPIA companies have already developed either antibodies as tools or assay formats to measure these in both pre-clinical and in clinical settings. Such antibodies and assays could be made readily available to the consortium participants to enable measurements of these new biomarkers to be qualified.
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 21 million for 3 target organs Ca. € 7 million per target organ: two clinical trials with serial sampling and subsequent bioanalysis (€ 4 million), sampling and subsequent bioanalysis from on-going Phases I, II III and IV studies (€ 2.5 million), assay development (€ 0.5 million)]
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The Applicant Consortium is expected to cover all three areas DIKI, DILI and DIVI. A translational approach is necessary to avoid duplication of methodologies. The regulatory authorities should be involved in this Applicant Consortium. The contribution from the Applicant Consortium should include all the aspects of the following general areas: Options for a qualification process: Such a process once made official and taken up by Health Authorities would facilitate the emergence of new qualified biomarkers for clinical use largely beyond the scope of this call. This would also help reduce animal trials by avoiding unnecessary re-testing in toxicology studies in case of safety signal. Markers having sufficient pre-validation data to give them a high probability of becoming “validatable”. Applicant Consortium members may know or have access to such new markers which would improve the predictivity of non-clinical safety studies and have a positive impact on

		attrition rates and drug development timelines. Such markers could also allow the reduction of animal trials by moving compounds faster to clinical phases. Clinical trials and samples: • identifying clinical unit(s) that could take the lead in implementing outcomes. • clinical units need to develop implementation plans in clinical studies which should include appropriate study populations, characterization of populations, sampling, assessment of current standards, standardization of current standards (including medical assessment), dosing regimens etc. • academics and clinics could investigate the specificity of the biomarkers with respect to drug induced pathologies but also investigate the utility of biomarkers to diagnose diseases. Biomarker assays: develop assays to enable measurements of these new biomarkers and study the sensitivity and specificity of these assays. Biologic/Mechanistic understanding: perform studies to understand the mechanism of these new biomarkers but also their potential limitations of scope.
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 15.0 million for this project.

6. Strengthening the Monitoring of Benefit/Risk

0	Topic Code	IMI_Call_2008_1_06
1	Topic title	Improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU
2	Project description	It is essential to have a thorough post-marketing surveillance system of marketed products to ensure a positive benefit: risk balance of medicines. In the past pharmacovigilance has tended to be a more reactive process focussing on spontaneous reporting, which was often insufficient to allow meaningful assessment due to under reporting and poor data quality There has been an important shift to a more proactive approach, requiring a broadening evidence base and a widening of expertise, resources and methodologies. The aim is to expedite the generation of more, and more reliable, pharmacoepidemiological data for proactive pharmacovigilance and risk management of medicines throughout their life-cycle. Observational research based on healthcare/claims databases (e.g. in the area of pharmacoepidemiology) currently pose difficulties with potential confounders and other methodological weaknesses that, in the past, have given rise to highly-publicised misleading results (e.g. observational studies on hormone replacement therapy, statin use and cancer, etc). The objective of a successful project under this call would be to develop, where appropriate, new methodology for healthcare/claims database studies and evaluate currently used methodologies, such as propensity scores and instrumental variables, that seek to address limitations of this type of research, specifically concerns about residual confounding or other forms of bias. Work should 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. Training aspects should be addressed where appropriate (link to the pharmacovigilance Education and Training call topic, page 95). Successful programmes should also include an approach to facilitate pan-European research by utilization of diverse national and multi-national data sources, resulting in data sets which are larger and more representative of the European population. This will increase confidence in the post-marketing monitoring of the benefit/risk balance of EU medicinal products, ultimately facilitating an earlier access of novel

		medicines to EU patients.
3	Key deliverables of the project	1. New methods of data collection in pharmacovigilance including methods for collecting data in the natural language and research on how to simplify data collection from reporters whoever they are. 2a. Evaluation of methods and development of operational definitions for signal detection and signal evaluation. Determination of these methods' performance characteristics and capacity for early detection of adverse events in spontaneous reports databases. If applicable, development of operational standards for screening algorithms and criteria to confirm or refute signals 2b. Evaluation of methods and development of operational definitions for signal detection and signal evaluation. Determination of these methods' performance characteristics and capacity for early detection of adverse events and identification of benefits in population-based epidemiologic data sources. If applicable, development of operational standards for screening algorithms and criteria to confirm or refute signals 2c. Establishment of methods for graphical expression of the benefit and risk of medicinal products using evidence from clinical trials, epidemiology studies and spontaneous reports. 3. Investigation and development of standards and processes for interoperability and sharing of European epidemiology data sources to determine their capacity for pharmacovigilance, signal detection, and large epidemiology studies for quantification of benefit and risk outcomes. The goal of this collaborative research is to enable a more rapid detection of new Adverse Drug Reactions (ADRs), as well as confirmation of safety and efficacy profiles of individual medicines and therapeutic classes of medicines, under 'real world' conditions. It will further help to develop risk management, establish and agree on new scientifically based and tested tools for the benefit/ risk assessment that will be used when establishing the benefit/risk profile of marketed drugs, rapidly investigate purported treatment-related risks and refute spurious associations between drug treatment and adverse events.
4	EFPIA participants in the project	Amgen, AstraZeneca, Bayer Healthcare, Boehringer-Ingelheim, Eli Lilly, Genzyme, GSK, Lundbeck, Merck Serono, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi Aventis, Sigma-Tau
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Expertise related to therapeutic area specific items and orphan drug issues • Data related to experience in a number of therapeutic areas to the extent that these data are non competitive (e.g. background rates in disease areas, Medical

		Information support etc) • Participation in projects for refining methods of signal detection based on state of the art expertise • Pharmacoepidemiologist resource • Statistical expertise • Expertise in Information Systems and Information Technology (IS/IT) • Project management resource
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 15 million
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	This consortium is expected to have participants from regulatory authorities, academia and small medium sized enterprises. The contribution from the Applicant Consortium is expected to include all aspects of the following areas. Development of analytical methods and algorithms for an enhanced detection and evaluation of safety signals: • using databases containing spontaneous adverse event reports • using claims/health care databases and other large sources of epidemiology data Creation of an infrastructure and services for the integration and interoperability of claims/health care databases across the EU to support: • pharmacovigilance monitoring and signal detection for single drugs and drug classes • large hypothesis-testing epidemiology studies that reflect the specificities of the EU population • the objective is not to create a new organisation, service or even a new database, but to develop and optimise methodology for observational PhV studies that will be applied in future to answer research questions on drug-related risks and benefits, utilising existing claims/healthcare databases across EU, and based on a common protocol. Observational research based on healthcare/claims databases (e.g. in the area of pharmacoepidemiology) currently pose difficulties with potential confounders and other methodological weaknesses that, in the past, have given rise to highly-publicised misleading results (e.g. observational studies on hormone replacement therapy, statin use and cancer, etc). This is partly because observational studies are necessarily not randomised and current methodology is often not powerful enough to address and eliminate

		confounding. The objective of a successful project under this call would be to develop appropriate methodology for Healthcare/claims database studies that would appropriately address limitations of this type of research. Development of methods – including graphical expression - for integration of safety profiles across all sources (clinical trials, epidemiology, spontaneous reports). Enhancement of early detection of new adverse drug reactions from marketed products and continuous monitoring of benefit-risk. Enhanced accuracy of signal detection and ability to differentiate true safety findings from spurious observations
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 11.0 million for this project.

IMI Efficacy Pillar

The objectives of the research activities within the Efficacy pillar are to address bottlenecks related to predictive pharmacology, the identification and validation of biomarkers and patient recruitment. Under the first call in 2008, the activities will focus on research in diabetes, brain and respiratory disorders. In addressing these topics it is expected to develop more relevant animal models, as well as early predictive clinical endpoints, in these diseases area though extensive translational medicine approaches.

7. Islet Cell Research

0	Topic Code	IMI_Call_2008_1_07
1	Topic title	Islet cell research: Improving β-cell function and identification of diagnostic biomarkers for treatment monitoring in diabetes
2	Project description	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, which are moderately successful in ameliorating fasting glucose levels, 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. In type 1 diabetes, the decrease in functional ß-cell mass is related to ß-cell loss provoked by an autoimmune process. In type 2 diabetes there is a progressive deterioration of ß-cell function and probably a concomitant drop in ß-cell mass. The mechanisms leading to these alterations are poorly understood. Moreover the molecular and physiological mechanisms of ß-cell function and renewal are far from being fully elucidated. Therefore the search for new therapeutic approaches aimed at maintaining and/or restoring the functional ß-cell mass requires a better knowledge of 1) the role of ß-cell function in health and disease, and 2) the mechanisms responsible for the decrease in ß-cell function and/or survival in diabetes. 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 type 2 diabetes as well as type 1 diabetes. In parallel, development of biochemical and imaging-based biomarkers of β-cell mass and function for early disease detection will facilitate the monitoring of treatment responses. Research will focus on molecular, physiological and clinical aspects of ß-cell function and turn-over, regulation and diagnostics covering the following areas.

		ß-cell dynamics in vitro and in vivo. Although impressive progress has been made in the past decade, the control of birth, life and death of a ß-cell remains largely an enigma. How do ß-cells develop and how is ß-cell mass regulated? Which are the progenitor cells that can differentiate into islet cells and what are the characteristics of the β-cell progenitors? As the major therapeutic goals for the future are prevention of β-cell loss, restoration of β-cell function and β-cell replacement, understanding the mechanisms that cause ß-cell loss in type 1 and type 2 diabetes is essential. To address these challenges studies will focus on: • Origin, source and function of novel ß-cells • Conditions for ß-cell proliferation and differentiation from precursor cells • Genetic and genomic studies for identification of biomarkers for responsiveness to drugs affecting ß-cell proliferation and differentiation • ß-cell apoptosis with emphasis on its mechanisms, prevention and methods of apoptosis measurement in animal models and in humans. The development of novel technologies, approaches and tools is required both in animal and human studies. Especially there is a need for: • Novel animal models and refinement of existing animal models to examine ß-cell proliferation in vivo. • Animal models that closely match the development of type 2 diabetes in humans with respect to ß-cell dysfunction and apoptosis • Novel biomarkers for ß-cell function and islet regeneration in vivo • Establishment of a standardized longitudinal cohort with a pre-defined population progressing, or not, to diabetes. • Non-invasive technologies for monitoring β-cell mass and function in patients and animal models. • In diabetic subjects, objective findings on ß-cell mass are very scarce and the time-course of ß-cell loss is lacking. The accuracy of β-cell mass determination by morphometric methods is hampered by a great variability in β-cell granulation in diabetes animal models. Therefore, novel non-invasive methods for monitoring of β-cell mass and function including new biomarkers, imaging and nanotechnological approaches are necessary.

		Cross talk of β-cells with other cell types (α-cells) in islets and with other tissues or organs ß-Cell physiology and function within the islet of Langerhans is the result of a permanent cross talk with other tissues and organs. In this regard, glucagon producing cells and endocrine cells of the intestine are of particular importance. Synthesis and secretion of insulin and glucagon act upon each other. Moreover glucagon can be considered as the hormone which antagonises insulin action on glucose metabolism especially in the liver and the ratio between the concentration of the two islet hormones is the main component of the control of glucose metabolism. • Research will include abnormalities in α cell function, α/β cell ratio, and the impact of α cell function on metabolic abnormalities in various stages of type 2 diabetes with special focus on α and ß-cells. The gastro-intestinal tract is an important source of hormones such as GLP-1 which has proven anti-diabetic effects. • The study of the interaction between intestine and pancreas will provide new insights into the generation of novel therapeutic approaches based on incretins. Impact of the project In the islet research field, the project will improve our understanding of the key mechanisms for ß-cell loss in type 1 and 2 diabetes and where research should be focused to reduce ß-cell loss by pharmacological agents. The project will also enhance understanding of ß-cell proliferation. This approach could provide novel therapeutic targets. There are already some commercially available compounds which have been shown to enhance ß-cell mass in vitro or in vivo in animal models of type 2 diabetes. Special focus will be on the understanding of the role of GI-derived ligands or signals towards the pancreas. For this reason it is important to develop non-invasive ways to measure ß-cell mass in order to monitor the progression of type 2 diabetes and how such progress can be arrested using novel pharmacological approaches. Maintaining and/or restoring the ß-cell mass will be beneficial for type 2 diabetic patients, only if the ß-cell function is concomitantly improved. The projects will lead to novel methods and diagnostic tools to measure the function of novel ß-cells and evaluate the functional maturity of the ß-cells including novel biomarkers and imaging techniques.

3	Key deliverables of the project	The key deliverables of the call will be in three categories: **Generation of tools:** • Identification and validation of industry-relevant cellular and animal models for proof of concept studies and for mechanistic studies aimed at defining the role of pancreatic β and α cells in diabetes. • Novel methods, including non invasive technologies and diagnostic tools, to measure function and mass of β-cells in vivo Novel well-characterised β-cell models and technologies to monitor β-cell function and mass, should improve our ability to predict in vivo outcomes with consequent 3R's benefits. **Identification and validation of biomarkers and targets.** • Through well defined protocols and techniques, discovery and validation of novel specific and mechanism-based molecular biomarkers for the characterisation of the progression of the disease. A translational approach will lead to a validation of such markers in both animal models and clinical trials. • Identification and validation of novel diagnostic approaches, including non invasive technologies, aimed at improving proof of efficacy studies in both experimental models and early clinical development. • Identification and validation of novel drug targets and novel pathways for intervention by combining genomics, transcriptomics, proteomics, bioinformatic and physiological approaches. **Knowledge:** • Improvement of our understanding of the key mechanisms for β-cell loss in Type 1 and Type 2 Diabetes • Understanding the mechanisms of β-cell proliferation and differentiation
4	EFPIA participants in the project	Amgen, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Merck, Novartis, Novo Nordisk, Roche, Sanofi Aventis, Servier, Solvay
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: **Pre-clinical contributions:** • DNA samples and samples for proteomics, genomics, immunoassays, cell based assays, in vivo studies, biomarkers (staff, laboratories, costs of reagents and materials). • Experimental models including cell lines, knockout and transgenic models, models of induced diabetes and

		metabolic disease. • Detailed protocols of relevant models and studies. Data from animal models characterised and validated with gold standard agents. • Technologies such as measurement of beta-cell mass, use of high content screening technologies, validation of targets using siRNA, and provision of proprietary pharmacological tools. • Database and informatics support for the integration of data and implementation of model systems. **Clinical contributions:** • Data from ongoing clinical studies exploring novel endpoints – both placebo and subject-treated with either proprietary (IP dependent) or marketed compounds. • Experimental clinical studies using tool compounds to investigate novel pathways or novel biomarker approaches. • Clinical trial management expertise and support. • Image analysis expertise and support. • Open/closed platform analysis of samples from pre-clinical and clinical studies.
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 10 million
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	Each Applicant Consortium is expected to develop a transversal approach addressing all points in the two main areas of research (β-cells dynamics and cross talk of β-cells). • Expertise and knowledge of pathophysiology and its application to new approaches to contribute to the generation of new ideas for a better understanding of molecular approaches to treatment of type 1 and type 2 diabetes. • Novel information on the conditions for ß-cell differentiation and proliferation to be exploited in further therapeutic developments. • Novel sources of β-cells with in-depth characterization of their physiology and regulation. • Identification of biomarkers in order to measure ß-cell mass and function during the course of diabetes and in response to diabetic therapies. • Novel animal models to examine ß-cell proliferation in

		vivo. • Non-invasive technologies for monitoring ß-cell function and mass. • Improved knowledge in islet cell physiology and pathophysiology and the cross talk of islet cells. • Novel pathways and targets for the regulation of ß-cell mass. • Novel insights in the interaction between intestine and pancreas to foster the generation of novel therapeutic approaches based on incretins.
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 7.0 million for this project.

8. Surrogate Markers for Vascular Endpoints

0	Topic Code	IMI_Call_2008_1_08
1	Topic title	Surrogate markers for micro- and macrovascular hard endpoints to shorten clinical trials on diabetes
2	Project description	The global prevalence of diabetes is currently 246 million people. Each year worldwide an additional 7 million people - or 13 persons every minute - will develop diabetes, and 3.8 million deaths are attributable to diabetes. In addition to human suffering, diabetes causes huge economic and societal costs mainly due to complications of the disease. These costs are largely the consequences of care and loss of productivity due to disability and premature death. In 2007, global health expenditure to treat and prevent diabetes totalled at least € 140 billion. 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 development of microvascular complications is related to poor glycemic control and duration of the disease. After 10 years of diabetes, over 70% of diabetic patients have some degree of complications. However, 10-15% of patients get these complications even if glycemic control is good, and another 10-15 % do not get severe complications even with poor control. Therefore factors other than glycemic control are involved in the development of microvascular complications. However, at the moment the data on these other factors are scanty. The most common macrovascular complication is atherosclerosis, which can lead to problems such as myocardial infarction or stroke. The prevalence of these complications is 2-3 fold higher in diabetic patients.. A number of factors, such as dyslipidemia, hypertension and poor glycemic control contribute to the development of macrovascular complications. While retinopathy and neuropathy significantly decrease the quality of life in diabetic patients, nephropathy and macrovascular complications are the factors which increase mortality. In the development of novel medications, it is important to demonstrate significant improvements in health outcomes, that is, both quality and duration of life. Since the development of complications in diabetic patients is so slow, real health outcome studies to test novel medications need to be very long. In addition, since we do not know all the factors which may contribute to complications, the number of patients to be included in these studies needs to be large. For these reasons, studies are very expensive, new information comes slowly and it takes a long time to develop medication to prevent or cure diabetic

		complications. There is a need therefore to develop ways to reduce the size and timelines for evaluating therapeutic efficacy on the establishment/ progression of micro and/or macrovascular complications. Research should focus on finding validated and scientifically justified biomarkers / surrogate endpoints for micro- and macrovascular hard endpoints in diabetes clinical research. Furthermore these efforts could help to classify or subgroup patients developing or suffering from micro- and macrovascular complications on the basis of biomarker profiles. This could enable sponsors of clinical trials to entertain more meaningful studies or identify patients who do or do not properly respond to a given therapy. A lack of animal models which can predict the development of diabetic micro- or macrovascular disease is a major issue in the development of novel therapies. It is even better if in vitro or in silico tools can be developed and validated to test the effect of novel therapies on diabetic micro- or macrovascular complications in patients. These new tools would reduce the size and duration of human studies. Good in silico models can reduce the need - or in the best case even replace - animal studies. These questions can be approached by analysing exiting data in already performed or in ongoing trials (a-c): a) Exploring data and samples from recent and ongoing landmark studies or other major databases. We should there be able to define and validate biomarker and /or surrogate endpoints for micro- and macrovascular complications. This database should include information on genotype, phenotype, biomarkers and outcome based on the previously performed studies. b) Assessing specific genotypes as biomarkers and/or surrogate endpoints for micro- and/or macrovascular disease. This can be done in DNA samples (when available) from large studies whose clinical results have been already reported. c) Assessing innovative assays and invasive and/or non-invasive imaging technologies to use as biomarkers for micro- and macrovascular disease. These questions can also be approached by performing novel studies (d-g): d) Testing in prospective randomized clinical trials compounds which influence glycemic control and monitoring the development of complications while collecting samples for genomic and biomarker analysis. This design will help to find and validate genomic and other biomarkers for complications. Another alternative is to perform observational studies, or a combination of both. e) Evaluating preclinical biomarkers /surrogate endpoints in different animal models that predict micro- and

		macrovascular disease in man. f) Developing in silico tools which can predict the effect of novel medications on micro- or macrovascular complications in diabetic patients. Predictive in silico tools would reduce the need for animal studies. g) Finding methods to prevent diabetes. Recently a major project (IMAGE) has been initiated with EU funding support for the prevention of type 2 diabetes. Other projects are ongoing for the prevention of type 1 diabetes. These projects will create a major database to characterize high risk individuals, who will or will not respond to preventive measures. These databases can be utilized to select patients for studies to test novel compounds designed for the prevention of type 1 or type 2 diabetes. The advantages of this two approaches strategy is that novel information can be found rapidly using existing data and available databases, and analyse samples made available for the first time to different stakeholders. The prospective studies can be used to validate this data. However, both of these can and should be started in parallel. The data in the already available databases will be analysed fast. This information can be used to direct, what kind of sample collection and analysis should be done in prospective studies. Strong co-ordination between these two approaches will be required.
3	Key deliverables of the project	The key deliverable of this project is to develop ways to make clinical trials testing novel medications on diabetic micro- and macrovascular complications shorter and more focused. This would provide several advantages: make trials cheaper, bring novel medicines faster to patients for the prevention and treatment of complications, and improve European competitiveness in clinical research. To develop predictive animals models for micro- and macrovascular complications would further reduce size and duration of clinical trials. In the best case, one can develop in silico models to reduce the need of both animal tests and clinical trials. Specifically, the project should deliver: 1. Validated industry-relevant, clinically meaningful and agency-acceptable biomarkers for micro- or macrovascular complications in both type 1 and type 2 diabetic patients. These biomarkers should be suitable to monitor progression, reduction or prevention of complications. With novel biological and information technologies, and new information from the disease, biomarker research can be extensive and it can also be rapidly expanded and redirected into the most appropriate areas of therapeutic need. There are already several biotechnology companies with well advanced technologies. 2. Validated genotypes of type 1 and type 2 diabetic

		patients who are prone to develop micro- or macrovascular complications, or who are less likely to do so. In the subgroup of patients prone to develop complications, genotypic studies can be further performed to identify responders and non-responders for novel preventive or therapeutic medications. This tailored medicine would save non-responders from potential adverse effects. 3. Novel assays and imaging technologies to detect biomarkers for micro- or macrovascular complications in type 1 and type 2 diabetic patients. As an example, a sensitive non-invasive imaging technology could reveal an atherosclerotic plague in its early stage. Such developments would shorten clinical trials and support the initiation of novel therapies faster. 4. Novel animal models, which predict the development of micro-or macrovascular complications in type 1 and type 2 diabetic patients. The refinement of preclinical models will increase their predictive power. The improved quality of preclinical data in drug development will reduce the number of studies required to support dose reduction and target validation. In addition, more predictive animal models would reduce the number of animals needed and the duration of in vivo studies. 5. Novel in silico models to test the efficacy and safety of novel medications in the prevention and cure of diabetic complications in man. In silico modelling can be fast, inexpensive and various models can be rapidly developed and redesigned when new information is available from the disease model or when novel medications are introduced. A successfully utilized in silico model can significantly reduce the need of animal studies and make clinical studies shorter and more focused. 6. A communication and training plan and target audience to implement the results effectively. It is important to publish the high quality data emerging from this research in journals with large readership and visibility. It will also be reported and discussed in major medical meetings. In addition, communication in the lay media about novel discoveries in the prevention or treatment of diabetic complications will be important for the image of pharmaceutical industry and scientific research overall. 7. The outcome of this research will deliver new tools for the development of therapies to prevent or treat an already huge and ever increasing issue – diabetic complications. To be able to utilize this information as soon as possible for the benefit of the patients, it is important that the new information will be discussed immediately with regulators for their complete

		understanding and approval. 8. Creation of a model for clinical research collaboration between key stakeholders (industry, academia, patient organisations, SMEs, etc).
4	EFPIA participants in the project	Boehringer-Ingelheim, Eli Lilly, Novo Nordisk, Pierre Fabre, Roche, Servier, Solvay
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Effective management and coordination of the work to deliver key objectives. • Data selection, statistical and bioinformatic expertise for the analysis of existing databases. • Clinical and preclinical trial planning and management, either directly by EFPIA member companies, or through outsourcing to Contract Research Organizations as appropriate. • Research protocols under GLP/GCP both for preclinical and clinical projects. • Organization of clinical trial in collaboration with academic investigators, using the resources of the EFPIA members, or outsourced to Clinical Research Organizations. • Marketed products to be used in clinical trials. Also compounds in current phase three of clinical development can be included in the different arms of the clinical trials, subject to need, respect for IP and agreement between the EFPIA companies. • Supply of New Chemical Entities (NCEs) (IP dependent) and pharmacological tools. The tools can include also novel devices for the delivery of NCEs or other emerging tools as appropriate. • Technical input regarding the sample collection and analysis. Sample collection may be outsourced, whereas the analysis will be done by EFPIA members and other partners. • Data management and informatics arising from investigation of existing databases as agreed by the partners, or from potential prospective studies. • Analysis of omics samples, potential biomarkers, DNAs etc. including data analysis. • Access to already existing clinical samples for studying biomarkers where applicable. Several major studies have already been conducted (UKPDS, BOTNIA etc), where a lot of data and clinical samples are available waiting to be further analyzed.
6	Indicative duration of the project	5 years

7	Indicative total in kind contribution from the EFPIA companies	€ 20 million
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Identification and making available databases and samples from previously performed or ongoing trials. Several large and long term trials have been performed examining the prevention of type 2 diabetes, identification of genomics and biomarkers of the disease as well as comparing treatments with different medications of type 2 diabetes (e.g. UKPDS, BOTNIA). In addition, studies for the biomarkers of type 1 diabetes have been ongoing for several years. To be able to utilize the already existing data and samples of these studies would be an important contribution of the consortium members who have been involved in these studies. • Exploration of the predictive nature of genotypes and early biomarkers. It is possible that this item may not be fully addressable within the duration of this call due to the long time it takes for the hard cardiovascular endpoints to develop. • Expertise in various areas of both preclinical and clinical research in order to propose innovative approaches to close the gap between animals and man. • Involvement of patient organisations appropriate for the long term clinical trials. Good access to appropriate patient organisations would speed recruitment, help to focus on specific groups and also reduce the drop-out rate.
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 14.0 million for this project.

9. Pain Research

0	Topic Code	IMI_Call_2008_1_09
1	Topic title	Pain research: Innovative preclinical and clinical rapprochement to produce biomarkers for safer and more effective treatments.
2	Project description	**Rationale:** 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. It is essential to build partnerships between academia and industry across the preclinical and clinical domains to accelerate the development of molecules for treating chronic pain conditions. Notably, we need 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, 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. **Mechanisms involved in generating and sustaining pain:** Understanding pain pathways and processes together with how they are modified by current analgesics provides an opportunity to develop better models (both preclinical and human), efficacy and stratification markers, all of which can help develop medicines targeting specific pain mechanisms underlying the pathophysiology. There is a need to understand: 1) how chronic pain is maintained, specifically in neuropathic pain where hyperalgesia and allodynia can persist in the absence of nerve injury. As such, increased insight is needed into the mechanisms underlying central sensitisation and its role in chronic pain; 2) how inflammatory mediators (either peripherally- or centrally-released), nociceptive neurone activity and central brain processes are involved in different types of pain; 3) how existing analgesics and new chemical entities (NCEs) modify inflammatory mediators, neuronal activity and plasticity, and alter function in key brain regions; and 4) the role of genetic factors in mediating and sustaining particular types of pain. **Preclinical animal model development:** The predictability of available animal models for chronic pain remains limited. There is a particular need for models that are translatable between man and animals, in terms of mechanisms and endpoints. This requires: 1) determination of the most predictive animal models; 2) removal of user-

		bias from accepted models and measures; 3) consideration of more complex nocifensive behaviour than simple withdrawal reflexes; 4) provision of greater coherence with emerging clinical techniques, for example, electrophysiological or imaging approaches; and 5) back-translation of markers validated in clinical studies of pain into appropriate predictive preclinical animal models. **Development of models and markers to translate pain outcomes and pharmacology between animals and humans:** There is a need to develop and validate mechanism-based human models of pain in patients, which could be standardised so that preclinical and clinical data-bases obtained with established analgesics, negative controls and NCEs could be compared, to characterise analgesic mechanisms and their PK/PD markers for preclinical and clinical use. Identifying and characterising functional or 'wet' markers that correlate with clinical efficacy will allow early identification of successful new analgesics as well as the ability to perform tailored clinical trials in subgroups of patients most likely to benefit. A thorough understanding of the genetic factors involved in particular types of pain will not only provide potential drug targets but also drive selection of candidate biomarkers. This will require whole genome scan hypothesis-free approaches in well-phenotyped patients. There is a need to identify and validate soluble mechanism-based plasma biomarkers for inflammatory pain and to further develop technologies with the potential to achieve translational pharmacology for CNS-penetrant drugs including, for example, quantitative EEG/evoked potentials, magnetoencephalography (MEG), PET, functional magnetic resonance imaging (fMRI), including arterial spin labelling [ASL], and diffusion tractography. The development of translational methodologies to assess both adequate biomarkers and PK in parallel would increase efficacy in early preclinical and clinical drug development. Proposals should focus on research programs aimed at identifying and characterizing a functional or 'wet' marker and its correlation to clinical efficacy, where a specific preclinical model or a human experiment will be compared to a specific clinical pain state, in order to demonstrate translational similarities, parallelisms or the lack of functional correlation. Methods could be genomics, imaging techniques or wet biological markers. PK/PD relationships could be highlighted. **Objective and quantitative assessments of pain for use in clinical trials:** It is important to be able to quantitatively detect analgesic efficacy in order to select the best treatment for a particular type of pain patient. More objective, quantitative measures of patients' pain are required and may emerge from newer

		developments in fMRI-determined brain activation of the pain matrix, EEG, MEG or other quantitative physiological responses. Such measures will require validation in randomised controlled trials using standard treatments and NCEs. Additionally there is a critical need to develop databases of well-phenotyped patients to enhance capability to perform clinical trials in these well defined groups. Finally, it is imperative that factors contributing to the placebo effects in analgesic drug trials are investigated in detail as large and variable placebo responses can increase the uncertainty in making definitive assessments of novel analgesic efficacy. Therefore, it is important to improve our understanding of the placebo response in a set of well-characterized patients. **Abuse potential:** More accurate prediction and understanding of signals of abuse potential in man is a significant goal in developing novel analgesics, many of which will act directly on brain receptors. The abuse potential of opiates makes this a particular area of concern. Imaging technologies have the potential to identify validated cerebral profiles of the positively reinforcing, psychostimulant properties of drugs of abuse.
3	Key deliverables of the project	1. Mechanisms involved in generating and sustaining pain: • Discovery of new mechanisms of central and peripheral sensitisation and of neuroplasticity involved in the development and maintenance of chronic pain. • Discovery through well-defined protocols and techniques of novel mechanisms of chronic pain in patients, which can be translated back to and further analysed in animal models. • Development of protocols and techniques (e.g. brain imaging) to analyse mechanisms underlying the placebo response in clinical trials on pain. 2. Preclinical animal model development: Development of predictive animal models of chronic/neuropathic pain (including pain in rheumatoid arthritis, HIV infection and cancer) focused on the following aspects: • Objective, quantitative and clinically translatable pain measures; • Methods enabling measurement of spontaneous pain; • Development of pain-free animal models of pain (including collateral behavioural markers that do not elicit pain). To this end, the following deliverables are expected: • Validated novel animal models (e.g. genetic animal models of type 1 and type 2 diabetes) • Validated novel pain measures in animals, devoid of

		elicitation of withdrawal reflexes, demonstrating sensory loss as well as hypersensitivity measures, and aimed at eliminating user bias in experimental pain assessment. • Adaptation of animal models of persistent and neuropathic pain in order to obtain, from anaesthetised rats, measures of fMRI and MRS-ROIs as CNS signatures/surrogate markers of pain. Development of techniques and methods to measure pain inside the NMR bore. Signatures of spontaneous versus stimulus-elicited pain. Compare and validate neuropathic pain models in different rodent strains and define biomarkers at different time-points following the inflicted injury, in order to find a correlation to biomarkers of the chronic pain patient. This approach should be combined with molecular profiling (genetics, transcriptomics, proteomics or metabonomics). 3. Development of models and markers to translate pain outcomes and pharmacology between animals and humans: Use of cerebral electrophysiological (EEG, MEG), brain imaging (fMRI, PET), "wet" biomarkers and molecular profiling (genetics, transcriptomics, proteomics or metabonomics) in animal models and in patients suffering chronic pain in order to identify brain mechanisms underlying chronic pain and to develop well-characterised translatable preclinical/human experimental pain models for decision-making and/or patient stratification. To this end, there is a need for improved preclinical-clinical translation of PK/PD data. 4. Objective and quantitative assessments of pain for use in clinical trials: • Refinement and extension of experimental clinical methods of objectively measuring pain, such as axonal neuronography (ectopic discharge) and quantitative sensory testing (QST). • Investigation of placebo effects in pain clinical trials by detailed review of placebo data provided by industry consortium members and extension to prospective studies investigating the placebo response. Also perform prospective studies investigating placebo response, especially in relation to study design issues. 5. Delineation of phenotypes of chronic pain patients: • Convergence of different methodologies (e. g., genetic linkage, QST, novel methods). • Correlated of treatment and/or disease progression with blood/plasma markers through providing access to a well-managed extensive sample collection of blood/plasma from animal models, healthy volunteers and pain subjects. • Delivery of reliable early efficacy signals through

		small-scale, stratified clinical studies. The project should focus on definition and characterisation of a pain phenotype, identification of patient cohorts and context validation of a relevant PRO for the specific studied chronic pain populations. 6. Brain imaging methodology that allows objective evaluation of the abuse potential of novel analgesics.
4	EFPIA participants in the project	AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Esteve, GSK, Merck, Orion Pharma, Pfizer, Pierre Fabre, Sanofi Aventis, UCB, Wyeth
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: Pre-clinical and clinical scientific expertise and the sharing of pre-clinical models, human experimental pain data and clinical trial data on non-proprietary compounds. **Pre-clinical contributions:** • Transgenic mouse strains/models • Established and novel animal models of chronic/neuropathic pain and behavioural measures • Competent support for surgical methods, behavioural analysis, and histology dealing with animal models of chronic/neuropathic pain • Together with companies specialized in clinical test apparatus of pain (e. g. quantitative sensory testing), design test apparatus for animal use in order to bring preclinical and clinical pain measures closer to one another. To this end, develop new technologies. • Expert support for electrophysiological and brain imaging characterisation of animal models of chronic/neuropathic pain • CNS and blood tissues from animal models of chronic/neuropathic pain for development of novel biomarkers • Access to biochemical biomarkers identified from pre-clinical models • Tool molecules (reference compounds) in order to characterise/validate animal models of chronic/neuropathic pain **Clinical contributions:** • Clinical trial management expertise/support • Clinical supplies of novel NCEs (depending on IP evaluation), pharmacological tools and marketed products • Data from ongoing experimental medicine studies aimed at novel, mechanistic and objective measures of chronic/neuropathic pain

		• Data on placebo response in clinical trials on chronic/neuropathic pain • Dependent on IP evaluation, effects of NCEs in clinical trials on chronic/neuropathic pain • Provision of appropriate support for clinical electrophysiological (axonography) and brain imaging facilities • Provision of tissue samples and biochemical biomarkers identified from preclinical and clinical studies
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 7.5 million
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	The Applicant Consortium is expected to address both pre-clinical and clinical aspects in chronic and neuropathic pain. Proposals submitted for funding should aim, where possible, to address an aspect of each of the main topics outlined above, ensuring the involvement of both pre-clinical and clinical scientists. An integrated approach employing imaging, electrophysiology, novel clinical measures and/or genetic/biochemical markers is desired. It is envisaged that academic partners will work closely with pharmaceutical partners. In addition to academic centres, the consortium is expected to benefit from the participation of patient organisations, regulators and imaging centres. The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Data and ideas about pathophysiology and disease mechanism as well as ways of measuring them. • Characterised cohorts of patients with well-described symptoms and clinical signs. These would be a historical resource for data mining, and should also be available for the consortium to undertake studies of genotype, plasma, imaging, electrophysiological or other functional biomarkers, to investigate the effects of pain challenges in patients and so provide linkage to results of healthy subject pain models that could better define the predictive value of pain models for efficacy in different symptoms and/or pain states. • Biobanks of samples from patients • Clinical data on human pain models, including placebo effect • Placebo effect data from clinical trials • Novel methods for assessing clinical pain in a more quantitative and objective way

		• Individual subject data from trials, to support development of in silico models exploring associations between phenotype, pain characteristics, drug effects and efficacy. If such clinical and in silico model databases exist, they could be brought in, as the consortium could greatly expand them. • Ability to combine and apply numerous areas of expertise e.g., behavioural assessment, brain imaging, electrophysiological and/or biochemical/genetic analysis • Infrastructure availability to house and breed transgenic animals
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 5.0 million for this project.

10. New Tools for the Development of Novel Therapies in Psychiatric Disorders

0	Topic Code	IMI_Call_2008_1_10
1	Topic title	New tools for the development of novel therapies in psychiatric disorders
2	Project description	**Background** The pathophysiological processes and etiologic factors in psychiatric disorders, depression and schizophrenia have so far proven elusive. Despite a growing understanding of the genetic determinants resulting in the development of these disorders, development of safe therapies that effectively relieve the cores symptoms or delays 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. The objective of this project is to leverage expertise and approaches in both diseases areas and to have a transversal approach. **Prediction of Treatment Outcome** Recent data show a correlation between gene expression (transcription) in human brain tissue and blood cells. This supports the hypothesis that transcription analysis from peripheral blood cells could provide relevant biomarkers for psychiatric disorders and response to treatment. A transcription pattern/metabolite/biomarker profile that predicts a favourable response to active treatments as well as placebo is the ultimate goal. **Relevance of Phenotype-Transcription Relationships** To facilitate selection of sub populations, transcription profiles/metabolite profile and genetic polymorphism should be related to a clinical phenotype. Therefore, the phenotyping should include a detailed description of symptoms, course of disease, previous and family history, environmental factors such as early and recent life events, medication history and co-medication, including drugs of abuse, personality traits and coping styles. **Gene and Metabolite Selection** The correlation between peripheral and CNS gene expression, at least for some of the genes, offers the possibility to align CNS transcription patterns in animal disease models with transcription patterns from homogenous patient populations. A similar approach can be used for metabolites. This approach will allow profiling of new compounds in preclinical models and will help advance targets/compounds based on their ability to modify clinically relevant markers in a direction consistent with a meaningful treatment response in

		humans. **Pre-clinical animal model development** In order to improve the preclinical assessments of putative novel medications, back-translational approaches driven by genetic or clinical observations, including human intermediate phenotype is essential to develop novel animal models more predictive of clinical efficacy. Wherever possible these models should employ endpoints aligned with endpoints used in clinical studies (e.g. PET, MRI, MEG and EEG) and demonstrate similar pharmacology to man such that PK/PD assessment and modelling can be used to support scaling to human efficacy.
3	Key deliverables of the project	Key deliverables of the project have been divided into four categories. **Identifications of transcriptional/metabolite/blood markers relevant for segmentation and stratification of patient groups** Analysis of transcription patterns and metabolites profiles associated with treatment response that can be used to select promising candidate genes for genotyping. Analysis of transcription patterns and metabolites profiles associated with treatment response that can to be used to better understand the disease biology and identify novel treatment targets. **Development of preclinical models that translate systems biology of disease** Development of preclinical models that validate signalling pathways/circuits identified in humans to reflect specific symptoms in schizophrenia or depression Development of animal model systems and identification of phenotypes or endophenotypes correlating to clinically relevant parameters. **Development of animal models that translate to clinical endpoints** Establish correlations between symptoms or disease modification and electrophysiological measures, MRI, blood/CSF measures in humans. Establish preclinical models that reflect the identified electrophysiological measures, MRI phenotypes and blood/CSF measures. Validate link between disease modification and changes in electrophysiological measures and/or MRI phenotype. Develop models of PK/PD relationships for pharmacodynamic markers. **Development of functional imaging and molecular neuroimaging paradigms for drug discovery in**

		depression and schizophrenia. Functional imaging: 1. Establish functional neuroimaging paradigms and readouts using MRI technology to measure pharmacodynamic effects of novel compounds at a given dose (e.g. using PK/PD modelling) 2. Investigate the predictive clinical relevance of functional neuroimaging paradigms and their role in early drug discovery Molecular neuroimaging: 1. Identification of novel PET ligand for specific central nervous system targets or receptors. 2. Synthesis and structure activity relationship (SAR) of BBB penetrant compounds with appropriate in vitro affinities and pharmacokinetics. 11C labelling of compounds, preclinical and clinical validation. 3. Development of computational methodologies for integrating receptor occupancy, pharmacokinetics and pharmacodynamic endpoints (RO/PD/PK models)
4	EFPIA participants in the project	AstraZeneca, Eli Lilly, GSK, Johnson & Johnson, Lundbeck, Novartis, Orion Pharma, Pfizer, Pierre Fabre, Roche, Servier, Solvay, Wyeth
5	Role of EFPIA participants in the project	In general it is expected that the EFPIA partners will contribute to the projects by providing neuropsychiatry expertise (preclinical and clinical). More specifically it is envisaged that the EFPIA will provide: **Preclinical contributions** • Access to, generation and phenotyping of genetically modified animals • Data from preclinical studies exploring disease models and translational markers (e.g. Electrophysiology, blood markers, transcriptional markers) • Supplies of NCEs and pharmacological tools • Synthesis methodologies for SAR evaluation • Toxicological evaluation of PET ligands **Clinical contributions** • Data from ongoing clinical trials of placebo/active control clinical trials (e.g. pharmacokinetics, pharmacodynamics, blood markers, Electrophysiology or MRI) • Clinical trial expertise • Clinical trial supply **Database Management** Generation and maintenance of Databases

		Clinical Trial & Project Management Knowledgeable and diligent project management
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 10 million
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	The Applicant Consortium is expected to address both pre-clinical and clinical aspects in depression and schizophrenia. The contribution from the Applicant Consortium is expected to cover all aspects of the following areas: • The consortium should consist of participants with complimentary expertises that will increase likelihood of synergy and that will result in successfully meeting two or more of key deliverable categories of the project within disease areas described in the call • The consortium should consist of both preclinical and clinical investigators • By an innovative project design, expertise and knowledge of the pathophysiology of the disease the consortium should lead to the generation of novel hypotheses for the treatment of major depressive disorder or schizophrenia and novel technologies for the early development of novel drugs The consortium should specifically: • Identify transcriptional/metabolite/blood markers relevant for segmentation and stratification of patient groups • Develop preclinical models that translate validated signalling pathways/circuits in humans • Develop preclinical models that translate to clinical endpoints • Develop molecular and functional neuroimaging paradigms for drug discovery.
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 7.0 million for this project.

11. Neurodegenerative Disorders

0	Topic Code	IMI_Call_2008_1_11
1	Topic title	Neurodegenerative disorders : Bridging the preclinical-clinical divide
2	Project description	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, pharmacodynamic models that allow early prediction of efficacy and markers to aid stratification of the patient population. The success of this will be dependent on the partnership of preclinical and clinical scientists to adopt an integrated approach to ensure effective translation of efficacy from bench to bedside and visa versa. This translational science/medicine approach will allow the rapid identification and accelerated development of successful candidate molecules as well as terminating efforts earlier on those unlikely to offer clinical benefit. **Healthy volunteer / Pharmacodynamic (PD) model development** Models such as scopolamine challenge, sleep deprivation and diurnal vigilance in the elderly have been used to mimic aspects of memory impairments characteristic of diseases such as Alzheimer's disease. However the decision-making capacity of these models is currently low due to lack of publicly available data (both positive and negative) and validation using a variety of cognitive enhancing agents with different mechanisms of action. In order to enhance our understanding of the molecular basis of these models and their application to drug discovery it is essential that these models are more rigorously explored using clinically proven memory enhancing agents. Key questions are 1) what is the most sensitive methodology for detecting pharmacodynamic effects in these models? To this end an integrated approach using a diverse range of techniques such as imaging, electrophysiology and cognitive measures will be required. 2) What is the predictive capacity of these models for efficacy in enhancing memory deficits in neurodegenerative disorders. **Pharmacodynamic marker development** The development of sensitive pharmacodynamic (PD) markers that are predictive of clinical benefit within weeks rather than months of treatment may not only reduce sample sizes required to define positive drug effect, but also accelerate progression from proof of concept to phase 2b/3. However the utility of these in clinical development is currently limited due to lack of extensive validation. Recently a number of promising pharmacodynamic markers such as rCBF, electrophysiology measures (e.g. ERPs), cognitive

		fMRI, MRS, novel neuropsychological tests, and peptides, inflammatory markers and altered metabolites in CSF or blood have been reported. Changes in many of these markers have been reported with doses of drug that are known to offer clinical benefit in patients, however for each end point pharmacological validation across different mechanistic targets is limited. There is therefore a need for these endpoints to be more fully validated by investigating the effects of a variety of agents with different mechanisms of action in a given disease population. Key questions are 1) what endpoints are the most sensitive to pharmacodynamic manipulation across a variety of different mechanistic targets? 2) what is the shortest duration of treatment required to detect a response? 3) how do drug exposure ranges required to drive the pharmacodynamic response compare to those required for clinical efficacy? 4) which if any of these PD markers provide good predictive capacity for ultimate clinical efficacy? 5) Can any of these pharmacodynamic endpoints be back-translated to detect pharmacodynamic responses in healthy young or elderly volunteers or indeed animal models. **Pre-clinical model development** Due to the complexity of neurodegenerative diseases and of the 'disease models' currently utilised within neurodegeneration research, together with the relative lack of 'gold standard' agents, it is generally accepted that there are few validated translatable models of disease. Indeed there are numerous examples where molecules demonstrating excellent efficacy in animal models subsequently fail to demonstrate any clinical efficacy. The reasons for this are far reaching, however, in order to improve the predictive capacity of animal models it is essential that we focus on developing new model paradigms that can be used to provide the necessary PK/PD information required to support dose predictions and translation of efficacy into man. To succeed in this arena is essential to develop novel models which reflect the basic pharmacological activity of the drug in addition to developing models more predictive of clinical efficacy using endpoints utilised in clinical studies. Some key questions are 1) what do we understand about the molecular target activity in preclinical species and man? 2) how is this changed in disease states? 3) how does our drug interact with its molecular target in preclinical species and in man? 4) what characteristics of disease progression can we measure in man – can we model and measure these in pre-clinical models using similar end-points? 5) are the endpoints used suitable for establishing a PK/PD relationship? Focus should be placed on back translation from the clinic identifying those aspects of human volunteer trials (HVT) and patient studies that can be taken back to the bench. Ideally pre-clinical studies should therefore be proposed in parallel to the clinical studies outlined above. Using similar standard agents, research programmes should be initiated to develop

		and validate PD markers/models and disease models, utilising translatable endpoints such as EEG, imaging and 'omics' markers. If successful, such models will not only support dose prediction (i.e. PK/PD) and the identification and validation of PD markers/models for use in Phase I studies but also develop models more predictive of clinically efficacy all of which will have a significant impact on the acceleration of drug development. Proposals submitted for funding within the areas of Alzheimer's disease, multiple sclerosis and Parkinson's disease should aim, where possible, to address an aspect of each of the main topics outlined above ensuring the involvement of both pre-clinical and clinical scientists. An integrated approach employing imaging, electrophysiology, novel clinical measures and 'omics' markers is desired.
3	Key deliverables of the project	Identification of, and pharmacological validation of parallel HVT and preclinical pharmacodynamic models to establish effective exposure ranges and support proof of mechanism studies: • Characterisation of HVT and preclinical pharmacodynamic models (e.g. sleep deprivation) using clinically validated agents • Identification of PD endpoints most sensitive to pharmacological intervention in HVT and preclinical models • Identification of model with highest predictive capacity of clinical efficacy Identification and pharmacological validation of novel in vivo animal models: • Development, validation and refinement of pre-clinical models using fully translatable endpoints and increased predictive capacity. This will improve the quality and ultimately the utility of preclinical data in drug development reducing the number of studies required to support dose predictions and target validation. • Identification and validation of pharmacodynamic markers to support preclinical and early clinical assessment in HVT/disease populations. • Validation of imaging, electrophysiology, serum/CSF/urine marker endpoints, and/or novel clinical measures with respect to their utility for assessing pharmacodynamic responses to drug • Identification of sensitive PD endpoints to support translation from animal to HVT and from HVT to patients • Identification of PD endpoints that most accurately predict clinically efficacious exposure ranges General: • Identification of PD markers to support internal decision

		making and regulatory submissions • Ability to design smaller, stratified clinical studies which deliver early signals of efficacy • Access to validated imaging facilities both clinically and pre-clinically with standardised protocols acceptable for regulatory submissions • Integrated approach to translational science/ medicine across academia and industry • Development of algorithms for combining diverse data sets such as EEG and cognitive endpoints • Access to a well managed extensive sample collection of blood/plasma from animal models, healthy volunteers and patients which can be correlated with treatment and/or disease progression • Standardised and validated protocols and data analysis methods across sites.
4	EFPIA participants in the project	AstraZeneca, Boehringer-Ingelheim, GSK, Johnson & Johnson, Eli Lilly, Lundbeck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Servier, Solvay, UCB
5	Role of EFPIA Participants in the project	The EFPIA participants will contribute: **Pre-clinical:** • Numerous transgenic mouse strains/models e.g. amyloid over-expressing mice. • Data from ongoing pre-clinical PD model development studies e.g. sleep deprivation • Data from ongoing pre-clinical/clinical studies exploring novel pharmacodynamic/cognitive endpoints e.g. electrophysiological and imaging characterisation of amyloid over-expressing mice • Animal models of disease including training in surgical skills, behavioural analysis and histological analysis required to run such assays • Archived tissues (CNS and blood) from animal models of disease to support genetic and/or biochemical/molecular analysis of novel biomarkers and correlation with disease onset • Access to biochemical biomarkers identified from pre-clinical models that could be replicated for validation in future studies • Primate model data e.g. aged primates, primate EAE • Biochemical assays developed and validated for use in humans, non-human primate and rodent models e.g beta amyloid assays. • Data from animal models characterised/validated with gold standard agents

		• Pre-clinical supplies of registered agents • Supplies of novel new chemical entities (NCEs) (IP dependent) and pharmacological tools • Open/closed platform analysis of samples from pre-clinical studies **Clinical:** • Data from ongoing clinical studies exploring novel pharmacodynamic/cognitive endpoints – both placebo response and subjects treated with NCEs (IP dependent) or marketed agents • Data from ongoing experimental medicine studies investigating HVT models with respect to response to registered cognitive enhancing agents and NCEs. • Placebo data sets from various clinical studies across Alzhiemer's Disease, multiple cclerosis and Parkinsons disease • Access to ongoing HVT/patient studies being conducted with NCEs where specific cohorts may be committed to imaging studies or samples harvested for biochemical biomarker analysis • Clinical supplies of registered agents • Supplies of novel NCEs (IP dependent) and pharmacological tools • Image analysis expertise/support • Clinical trial management expertise/support • Access to biochemical biomarkers identified from clinical patient studies that could be replicated for validation in future studies. • Open/closed platform analysis of samples from pre-clinical and clinical studies **General Project Management:** In addition to providing general neurobiological expertise/input into the project, it is envisaged that EFPIA partners will work closely with public partners to ensure effective management and coordination of work to deliver key objectives.
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 7.5 million

8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	Using an integrated approach to translational science/ medicine the Applicant Consortium consisting of both pre-clinical and clinical scientists should aim to exploit similarities in the different diseases areas mentioned in this proposal to develop better HVT models, pharmacodynamic markers or animal models to support clinical development across disease areas. The contribution of the Applicant Consortium is expected to address all aspects of the following areas: • Develop models which have the ability to combine behavioural assessment, imaging, EEG and/or biochemical/genetic analysis from both pre-clinical and clinical studies. • Identify and validate PD markers to support pre-clinical development, internal decision making and regulatory submissions • Identify and validate HVT models and/or pharmacodynamic markers which provide the ability to design smaller, stratified clinical studies which deliver early signals of efficacy • Establish validated imaging facilities both clinically and pre-clinically with standardised protocols and data analysis methods acceptable for internal decision making and regulatory submissions
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 5.0 million for this project.

12. Understanding Severe Asthma

0	Topic Code	IMI_Call_2008_1_12
1	Topic title	Understanding Severe Asthma, the fundamental bottleneck to advancing new medicines for the syndrome
2	Project description	Asthma is an inflammatory disease of the airways with a high health care and patient burden. 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. The patients with severe asthma remain symptomatic with lung function impairment and poor quality of life despite combined treatment with the highest doses inhaled corticosteroids and long-acting bronchodilators as well as other medications. A significant proportion of the patients with severe asthma in fact remain “uncontrolled” whilst in addition receiving chronic treatment with oral corticosteroids. The terms “difficult asthma” and “refractory asthma” are also used to describe this patient group. Altogether, severe asthma is a heterogeneous syndrome comprised of many different clinical manifestations such as patients with frequent exacerbations, chronic progressive airflow obstruction, or near-fatal attacks. Differences in clinical course presumably reflects different phenotypes with distinct pathobiologies. It has been estimated that the 10% of asthmatics with the most severe disease account for up to 50% of the total societal costs of asthma (direct and indirect costs). Given the above considerations, it is clear that the greatest unmet need for new asthma medicines is for patients with severe disease. Discovery, research and development of new treatments for patients with severe asthma, presents clear challenges which include: • Although experts at specialist centres generally agree on diagnostic criteria emphasising the incomplete response to current treatments after long-term specialist follow up, there is a need for effective use and further development of these diagnostic criteria for mechanistic and therapeutic trials, an obligatory requirement to identify and characterize patients or credibly study them • Lack of understanding of the natural history and disease mechanisms in the setting of disease heterogeneity, including its frequent comorbidities, and biochemical and genomic biomarkers to identify patient characteristics associated with different phenotypes/genotypes • Without better understanding of disease etiology and pathogenesis, relevant preclinical and clinical models cannot be developed to enable translational research strategies. This hinders identification of efficient and

		relevant targets and developing new therapeutics for patients with severe asthma • Development of novel agents as maintenance therapies requires considerable investment, especially for long and large complex clinical studies. Hence there is a need for validated and broadly accepted (also by Regulatory Agencies) biomarkers which are predictive of clinical outcomes. Availability of validated surrogate markers will increase efficiency in the clinical development process. • The current uncertainty regarding which are the relevant outcomes for patients with severe asthma (e.g. physiological parameters including bronchial reactivity assessments, patient related outcome measures, clinical endpoints like exacerbation) needs to be addressed. It needs to be worked out what are the optimal study designs and follow-up times; and whether measures and results that apply to mild asthma also apply to severe disease The Innovative Medicines Initiative (IMI) strategic agenda recognizes these needs and challenges, giving explicit recommendations for relevant research. It is clear that the critical issue is a lack of understanding of the different phenotypes and genotypes of disease for patients with the syndrome severe asthma. Without addressing basic questions of etiology, pathogenesis, patient characteristics, risk factors, specific phenotypes and genotypes, one cannot find solutions to key bottleneck issues related to biomarker and target identification, as well as develop relevant translational models or outcome assessments. There are established academic groups within the EU that have been working on areas related to our understanding of asthma. These groups have however only received fragmented and small-scale funding from previous EU Framework programmes (FP4-6). Hence the call for 2008 is to build an EU Severe Asthma consortium focused on disease understanding. The intent will be to harness efforts of already established groups that are presently working independently. The proposed consortium should include expertise both with adults and children with severe asthma. The requirement for the consortium is to establish diagnostic criteria, define relevant phenotype and genotype markers, and set up a large longitudinal patient cohort which will act as a central platform to enable understanding of severe asthma. The severe asthma cohort ultimately will enable scientific research leading to validation of novel biomarkers and clinical measures/ outcomes, and will serve as a vehicle to develop relevant translational models The severe asthma patient cohort can be built through establishment of a common protocol for patient

		identification and assessment together with a common database or prospective registry which will enable:
		• EU and global agreement by scientific as well as regulatory bodies on definition, diagnostic criteria and standard investigative procedures for patients with severe asthma
		• Longitudinal patient study and associated sampling for phenotype and genotype markers of disease progression
		• Multi-disciplinary approach to new technology / technology platform development to support the identification of markers for:
		  • defining patient selection
		  • enabling early (and differential) diagnosis
		  • disease progression
		  • drug effects
		• Multi-disciplinary approach to new technology / technology platform development to support the monitoring and follow up of patients with severe asthma in Europe.
		• Further application of 'omic' technologies in a systems context to support biomarker identification and validation
		• Build understanding of aetiology and pathogenetic. mechanism of asthma exacerbation, enabling the identification of new targets and therapeutic approaches.
		• Access to defined patients which will facilitate enrolment and study of patients for clinical trials by academic and pharmaceutical research.
		• Develop study protocols with effective and validated end-points for different severe asthma phenotypes (e.g. frequent exacerbators versus persistent severely obstructed).

3	Key deliverables of the project	Improved understanding and diagnostic definition of severe asthma, leading to: • EU and globally agreed (ERS/ ATS as well as regulatory agencies) diagnostic criteria for severe asthma. • A longitudinal cohort of patients with severe asthma who have been characterised (including relevant phenotype and genotype) in a standardised way using a common protocol, data collection and database, with flexibility for novel measures to be added-in during the life of the project. • Identification as well as subsequent validation of novel

		targets for pharmacological intervention and biomarkers to assess pharmacological response or predict effects on clinical outcomes including disease progression or for diagnostic purposes. • Identification of targets relevant to specific phenotypes or genotypes of severe asthma. • Understanding of aetiology and pathogenesis of asthma exacerbations as mechanism to identify new targets and therapeutic approaches especially with regard to delaying time to exacerbation and reducing severity of exacerbation, which ultimately will deliver significant pharmacoeconomic benefits. • Accurate targeting of an intervention to a particular, well-defined patient sub-population. • Capability to develop translational models for appropriate prediction of clinical relevance through preclinical modelling. • Access to defined patients which will facilitate enrolment and study of patients for clinical trials by academic and pharmaceutical research.
4	EFPIA participants in the project	Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Merck, Novartis, Pfizer, Roche, UCB
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Project management • Clinical FTE for protocol and CRF technical input and development and clinical monitoring of the project in the field • Technical input and resources related to assays, imaging and application of other technologies • Database and informatics support • Statistics expertise • Facilities and management of biobank for tissue samples • Coordinate input from key stakeholders where relevant e.g. ERS/ ATS, EMEA, patient organisations
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 12.5 million
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Access to patients with severe asthma, ability to characterise the phenotype and genotype of these patients

		• Develop study protocols with effective and validated end-points for different severe asthma phenotypes (e.g. frequent exacerbators versus persistent severely obstructed). To include longitudinal patient study and associated sampling for phenotype and genotype markers of disease progression
		• Establish common database/ prospective registry of patients
		• Tissue bank (“biobank” for e.g. bronchial biopsies, lung tissue, sputum, BAL or bronchial washings)
		• Multi-disciplinary approach to new technology / technology platform development to support the identification of markers for
		  • defining patient selection
		  • enabling early (and differential) diagnosis
		  • disease progression
		  • drug effects
		  • monitoring and follow up of patients with severe asthma in Europe.
		  • develop assays to enable measurements of these new biomarkers and study the sensitivity and specificity of these assays.
		• Understanding of aetiology and pathogenesis of asthma exacerbations as mechanism to identify new targets and therapeutic approaches.
		• Access to defined patients which will facilitate enrolment and study of patients for clinical trials by academic and pharmaceutical research.
		• EU and global agreement by scientific as well as regulatory bodies on definition, diagnostic criteria and standard investigative procedures for patients with severe asthma

9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 9.0 million for this project.

13. COPD Patient Reported Outcomes

0	Topic Code	IMI_Call_2008_1_13
1	Topic title	COPD Patient Reported Outcomes (PROs), a major bottleneck to understanding patient and economic benefits of new therapies.
2	Project description	**Background:** 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. It is currently the 4th leading cause of death among chronic diseases and is projected by WHO to be the third leading cause by 2020. It is also an increasing cause of chronic disability in the European community, placing a huge and increasing burden on health care resources. Demonstration of efficacy of new therapy has relied on demonstration of reduction of airflow obstruction. There is now a clear understanding that this does not capture the potential benefits that the patients experiences. **The need:** Capturing the COPD patients' experience of the disease and effects of treatment is an important aspect of evaluating treatments for COPD. The Regulatory - CHMP -guidelines in Europe recommend the use of symptom endpoints, in addition to lung function measurements, for evaluating treatments for COPD. The 2008 call will focus on Patient Reported Outcome (PRO) tools to be used in clinical trials to evaluate treatments for COPD (Chronic Obstructive Pulmonary Disease). **Issues:** 1. A patient with COPD experiences a variety of symptoms; a key symptom is dyspnoea (shortness of breath). 2. Symptoms of COPD restrict patients' ability to perform daily activity and also results in psychological consequences resulting in significant impairments to overall health status. 3. COPD patients also experience acute worsening of their symptoms- exacerbations- that often require a change in their treatment, sometimes even requiring hospitalization. 4. All these are potentially important aspects to measure when evaluating outcomes of treatments for COPD. 5. The limited number of scientifically developed and

validated patient-reported outcome (PRO) measures that meet regulatory requirements have resulted in difficulties in providing solid evidence on these outcomes that reflect the patients' perspective on product label claims.

6. A PRO is any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy. PRO Measurement tools should be generated with adequate patient input.

Scope:

1. The pharmaceutical companies supporting this IMI call propose that the efforts focus on the selection or development and validation of PRO tools that will facilitate the measurement of outcomes that appropriately capture patients' experience of the disease and the impact of treatment.
2. This will involve the selection/development and validation of measurement tools that are sensitive to pharmacological interventions and can predict pharmaco-economic benefit ~ especially for the quantification of exacerbations and functional performance.
3. The work will encompass the European Regulatory agency (EMEA) guidance and their futures needs
4. The work will integrate with International programmes that are developing PROs for COPD to lead to global instruments through shared knowledge and practice

For 2008, the call for COPD is to request proposals that speak to these needs and which will be planned in two phases:

Phase A: Develop a framework to understand the Patients experience of COPD, especially in the European context, to inform strategies to measure outcomes meaningful to patients in global clinical trials

Phase B: Develop/select and validate PRO measurement tools, to use in clinical trials evaluating treatments for the disease.

It is anticipated that the two phases will run sequentially, though some activities may need to be conducted in parallel to facilitate timely progression of the project.

Phase A: Developing a framework to understand the Patients experience of COPD

The initial phase of the project may include an extensive review of literature to identify areas that have been found to be important to COPD patients. This could help to draft methods for more qualitative explorations (via focus groups, interviews) with patients. A thorough review of patient based outcome measures used in the area will also need to be

		conducted. Qualitative work may require to be conducted in different countries with a view to identify any nuances resulting from cultural or linguistic differences. a) A comprehensive model will be developed that includes the various aspects/concepts that help characterize the patients' experience of the disease. b) Conceptual frameworks for some of the most important issues that are identified by the patients. These frameworks would help to identify the measurement targets and in turn, the selection of existing measures (or the need to adapt/modify existing tools) or the need to develop a new tool in the absence of existing measures. c) A report of the review of patient based outcome measures in the disease area to facilitate selection of the tools and/or to inform the construction of items for a new tool. At the end of phase A, it is anticipated that there will be formal discussion of findings with all project participants including EFPIA companies, academic bodies, patients organisations and Regulatory agencies, to facilitate next steps. **Phase B: Selecting/Developing and validating PRO measurement tools to use in clinical trials.** The development of a PRO tool is a complex process that involves varying sequence of events, simultaneous processes and iterations. Once a tool is developed based on work performed in Phase A, including a conceptual framework, its psychometric properties- reliability, validity, responsiveness to change- needs to be established. There is also the need to define the scores from the tool that would define a clinically important change/ responder. It is anticipated that development and validation of new PRO measures would follow the following sequence: a) Adjust conceptual framework and draft instrument, including method of administration, format, recall period, response options, cognitive interviews, pilot test, documentation of content validity. b) Confirm conceptual framework and asses other measurement properties, including scoring rule, score reliability, construct validity, ability to detect change. Finalise format, content, scoring, procedures, training materials, Document measurement development. c) Collect, analyse and interpret data, including protocol preparation and statistical analysis plan with final endpoint model and responder definition. Collect and analyse data. Evaluate treatment response using cumulative distribution and responder definition. Document interpretation of treatment benefit in relation to claim. d) Modify instrument based on findings from above. Translate and culturally adapt to other languages.

		Harmonizing efforts to support global clinical trials In the US, there is an initiative in collaboration with the FDA to develop a new PRO instrument for COPD exacerbations (EXAcerbations of Chronic pulmonary disease Tool for Patient Reported Outcomes or EXACT-PRO). There are also potentially other initiatives that are being proposed in the US in the area of COPD outcomes. There are lessons from Rheumatoid arthritis (RA) that PRO development should not come from two sources e.g., there are 2 PROs for RA trials; ACR (American College of Rheumatology) and associated groups in the US and ILAR (International League of Associations for Rheumatology) in the EU. This has resulted in the need for studies to use both sources of PROs or to conduct separate European and US studies. Any new PROs for COPD should therefore be developed in such a way for acceptance in both the regulatory authorities for Europe and US, i.e., EMEA and FDA. Active collaboration/input from the European agencies and the FDA will be sought. New technology will be used such as electronic data capture for the PRO assessments. The final stages would be the application of the questionnaire/instrument to be used by the Industry partners in phase II and III studies.
3	Key deliverables of the project	**Phase A** • A comprehensive model that includes the various aspects/concepts that help characterize the patients' experience of the disease. The model could also include the relationships among the various concepts. This model will help researchers identify the outcomes to be considered as endpoints in clinical trial evaluations of new treatments. • Conceptual frameworks for some of the most important concepts that are identified by the patients. These frameworks would help to identify the measurement targets and in turn the selection of existing measures or the need to adapt/modify existing tools or the need to develop a new tool in the absence of such existing measures. • A report of the review of patient based outcome measures in the disease area to facilitate selection of the tools and/or to inform the construction of items for a new tool. **Phase B** • At least two new and fully validated Patient Reported Outcome measures that can be used in clinical trials,

		using an electronic format, for evaluating COPD treatments to support label claims that reflect the patients' perspective of the disease and treatment. • Introduction of electronic capture devices for the PROs with validation of the devices and data acquisition. • The adoption of a global exacerbation PRO that would be fully validated for use in the major markets of the world. • To share and to train in the use of the PROs to enable further validation in clinical trials of COPD therapy
4	EFPIA participants in the project	Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Merck, Novartis, Pfizer, UCB
5	Role of EFPIA participants in the project	The EFPIA participants in the project will contribute: • Project management to organize the validation work and overall delivery, including a plan for consortium management. • Outcome Research Scientists and clinical scientists. They will contribute to the development in both phase A and phase B, including relevant framework and protocol development and monitoring of validation studies. • Technical input on statistics and database management. • Provision of relevant hardware for home monitoring and electronic data capture. • EFPIA will interact with the relevant regulatory authorities globally. • Application and data management/ reporting of the questionnaire/instrument in phase II and III studies.
6	Indicative duration of the project	Phase A - 1 year Phase B - 5 years (a part of phase B could commence in parallel to phase A to facilitate timely collaborations)
7	Indicative total in kind contribution from the EFPIA companies	Phase A - € 2 million Phase B - € 8 million
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	In addition to academic centres, patients organisations and regulatory authorities should be involved in this Applicant Consortium. The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Expertise in PRO development and validation together with knowledge of EU and US regulatory standards for PROs. • Selection/development and validation of measurement tools that are sensitive to pharmacological interventions and can predict pharmaco-economic benefit ~ especially for the quantification of exacerbations and functional

		performance.
		• Phase A: Developing a framework to understand the Patients experience of COPD
		  • Literature review and report including patient based outcome measures used in the area to facilitate selection of the tools and/or to inform the construction of items for a new tool.
		  • Qualitative work (via focus groups, interviews) with patients. Work may require to be conducted in different countries with a view to identify any nuances resulting from cultural or linguistic differences.
		  • A comprehensive model that includes the various aspects/concepts that help characterize the patients' experience of the disease with objective to identify the outcomes to be considered as endpoints in clinical trial evaluations of new treatments.
		  • Conceptual frameworks for some of the most important concepts that are identified by the patients to identify the measurement targets and in turn, the selection of existing measures (or the need to adapt/modify existing tools) or the need to develop a new tool in the absence of existing measures.
		• Phase B: Selecting/Developing and validating PRO measurement tools to use in clinical trials
		  • Adjust conceptual framework and draft instrument, including method of administration, format, recall period, response options, cognitive interviews, pilot test, documentation of content validity.
		  • Confirm conceptual framework and asses other measurement properties, including scoring rule, score reliability, construct validity, ability to detect change, finalise format, content, scoring, procedures, training materials, document measurement development.
		  • Collect, analyse and interpret data, including protocol preparation and statistical analysis plan with final endpoint model and responder definition. Collect and analyse data. Evaluate treatment response using cumulative distribution and responder definition. Document interpretation of treatment benefit in relation to claim.
		  • Modify instrument based on findings from above. Translate and culturally adapt to other languages.
		  • Undertake full prospective validation of the instrument and share the information to enable use as a secondary outcome measure in clinical trials.
		• Harmonize with international efforts to support global clinical trials e.g. US based initiatives and aim for acceptance by both the regulatory authorities for Europe

		and US, i.e., EMEA and FDA. • Application of new technology such as electronic data capture for the PRO assessments
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 7.0 million for this project.

IMI Education & Training Pillar

The Education & Training Pillar has identified a number of gaps within education & training in support of the medicines development process. In order to address this gap a number of activities are proposed in 2008 which include the establishment of a European Medicines Research Training Network and the development of training programmes in safety sciences, medicine development and pharmacovigilance. This call shall therefore support the education and training of current and future professionals involved in biomedical R&D. Furthermore, the proposed training scheme provides the basis for information on the medicines development process to stakeholders who are not directly involved in the process, such as members of research ethics committees, journalists, venture capitalists and patients.

14. European Medicines Research Training Network

0	Topic Code	IMI_Call_2008_1_14
1	Topic title	Establishment of a network to facilitate and coordinate European training and education relevant for stakeholders of medicines research and development
2	Project description	The pharmaceutical industry needs highly skilled professionals who understand cutting edge technologies and life sciences 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. Unfortunately uptake of new science in academic teaching is not happening quickly enough. As a result of this some companies have individual initiatives to establish training courses to address their needs, others simply relocate to where they have access to the right skills. However, these initiatives are typically local and do not address the problem from a European strategic perspective. If this problem can be addressed on a European level it will increase the critical mass of scientists underpinning the industry, and consequently Europe will be increasingly attractive for industry as they make decisions on where to locate and/or expand their R&D facilities. To address this, a mechanism is needed to ensure that industry and academia cooperate on courses that are designed and implemented rapidly. Industry input is needed because they are the in the forefront of science when it comes to drug development, and companies collate emerging technology areas to drive their businesses. This partnership should ensure training to support the pharmaceutical industry in a timely fashion and facilitate continuing professional education and development. In addition, various groups could benefit from being better informed about the conditions for the development of medicines, the pharmaceutical industry and its value proposition, e.g. patients, ethical reviewers, journalists. This would allow them to engage with industry in a better way to

		benefit all parties. IMI aims to 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. Because science and industry's needs constantly evolve, training courses must be evaluated and updated on a regular basis. It is a challenge to anticipate emerging training needs and provide appropriate training solutions, for the biopharmaceutical sector. A European approach, gathering industry, universities and other stakeholders active in biomedical/biopharmacetical training is necessary to develop a sustainable solution to close existing training gaps
3	Key deliverables of the project	Create, develop and coordinate a network with the goal to facilitate identification and exploration of options for efficiently responding to existing and emerging training and education needs within cutting edge technologies and life sciences disciplines related to medicines research and development. Design a plan to address the before mentioned issues 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.
4	EFPIA participants in the project	Almirall, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Chiesi, Eli Lilly, Esteve, Genzyme, GSK, Johnson & Johnson, Lundbeck, Merck Serono, Merck, Novartis, Novo Nordisk, Orion, Pierre Fabre, Pfizer, Roche, Sanofi Aventis, Servier, Sigma-Tau, UCB.
5	Role of EFPIA participants in the project	The EFPIA participants will provide: • Identification of gaps in skills and definition of training courses to address these gaps in collaboration with academia to ensure an ongoing common understanding of the emerging technologies and industry's training needs • Definition of the format for industry training and sharing of existing training materials and case studies • A consultative role in the set up, development and management of the training coordination • Input to the business course • Lecturers for the courses • Work placements and mentors • Access to facilities • Support to an IMI PhD - level programme for PhD fellows in the companies

6	Indicative duration of the project	7 years
7	Indicative total in kind contribution from the EFPIA companies	€ 5 million
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: Set up, in collaboration with industry, a network of research training centres with the goal to identify and explore the options for efficiently responding to the existing and emerging biopharmaceutical training needs. The network should have an anchoring structure in European universities to enable academic input and to facilitate industry-academic collaboration. The Applicant Consortium shall contribute: • A plan to coordinate and administrate this network that includes an initial number of core institutions • Establish a strategy for a process to extend /enlarge the initial network to ensure pan-European coverage • The network should support the IMI PhD - level programme for PhD fellows in the companies and develop a pan-European (alumni) network. • Innovative, approaches on the organisation of the network and its programmes • Proposed timelines for the establishment of the network and its programmes including decision points • Develop a strategy to establish a European biopharmaceutical research training network for the organisation of training courses on emerging science and technologies that can be made rapidly available across Europe. A plan for a structured approach for anticipating training needs on emerging science and technologies.
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 4.0 million for this project.

15. Safety Sciences for Medicines Training Programme

0	Topic Code	IMI_Call_2008_1_15
1	Topic title	IMI Safety Sciences for Medicines Training Programme
2	Project description	Contemporary safety evaluation during development of medicines comprises pre-clinical safety assessment in animals and clinical safety assessment in humans. One of the bottlenecks identified in the IMI SRA relate to the low predictability of preclinical safety testing leading to expensive late phase attrition of drug candidates and potential risks for humans. A translational aspect of safety assessment is missing. A new breed of scientists, safety scientists, with a much broader spectrum of knowledge than the traditional toxicologist, is 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, mammal 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. The programme is aiming to raise the competence level of industry and regulatory agency specialists in safety assessments. This should lead to increased safety for humans and decrease late phase attrition of drug candidates due to safety issues. Post graduate courses within the fields of toxicology (preclinical) and clinical human safety pharmacology exist in Europe and are provided by universities and commercial course providers. However; currently no courses exist which addresses the translational aspects of the safety scientist as described above. To address this, an IMI training programme at Masters level should be developed. The project comprises 2 phases: Phase 1, Establishment of the training programme, 1 year Phase 2, Deliver the training programme, 4 years Halfway through the 5 years programme, the IMI training programme must be evaluated to ensure satisfaction from course participants, industry and other users of the programme. • The task is to establish and run a programme to train scientists holding a degree in life sciences to become experts 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. • The programme must address relevant scientific,

		regulatory and ethics issues • The programme should address the societal interpretation of medicines safety, e.g. with input from patient organisations • Faculty should consist of teachers from academia/industry/regulatory • The programme should be modular to ensure flexibility and to cope with future scientific development • The programme should include a combination of lectures and workshops and should enable distance learning assuming that participants continue their normal work • Each topic should be completed with case studies related to a concrete safety issue (e.g. a case from the student's institution) • The programme should comprise the equivalent to the workload of a full-time student during one academic year; however it should be possible to enlist on a part time basis to complete the programme within 2 to 3 years • Option for scientists to pursue or complete single topics / modules (continuing professional development)
3	Key deliverables of the project	• A new breed of scientists capable to translate from classical pharmaceutical toxicology to human safety pharmacology and by this provide better input to portfolio decisions to reduce late phase attrition due to safety issues and to improve safety to humans in clinical trials. • A programme for multidisciplinary training of scientists involved in the safety evaluation of medicines in development • A European Network of Faculties (universities and private institutions) able and willing to support the project • A Coordinating Board, comprised of members belonging to the various stakeholders of E&T in Safety Sciences in Europe, ensuring the external validity and practical application of the proposals, as well as the adequacy of contents and solutions proposed • Pan European criteria to ensure consistency of the training efforts in the field of science graduate of the pharmaceutical industry • The programme will be evaluated based on the number of course participants
4	EFPIA participants in the project	Almirall, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Chiesi, Eli Lilly, Esteve, Genzyme, GSK, Johnson & Johnson, Lundbeck, Merck Serono, Merck, Novartis, Novo Nordisk, Orion, Pierre Fabre, Pfizer, Roche, Sanofi Aventis, Servier, Sigma-Tau, UCB.

5	Role of EFPIA participants in the project	The EFPIA participants will provide: • Input on the needs of the industry for the content of the course • Lecturers for the courses • In house mentors for the companies' students • Provision of case studies • Provision of short term tutoring programmes in an industry environment • Provide input to members of the consortium on new scientific ideas and technologies
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 3 million covering 25 EFPIA employees and senior staff members as members of faculty over the 5 year period • EFPIA employee's participation in course development • Senior staff members to be members of faculty for lecturing and as assessors • Preparation for lectures • Travelling and accommodation in connection with lectures • Development of case studies • Sharing existing relevant in-house training programmes and/or educational materials • Facilitation of training by creating/maintaining recognised "training positions" in the companies with adequate support of in-house mentors • Hosting courses/modules, lecture rooms & facilities • Paying all course fees and expenses for employees participating in the programme
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	The contribution of the Applicant Consortium is expected to include all aspects of the following areas: • The programme should map and utilise established courses providing the necessary content and new courses developed by the consortium • Plan to organise, set up and deliver the programme • Description of the content of the course modules and requisites for quality assurance measures • Involvement of academic centres in European areas where needed (likely new accession countries) • Innovative, realistic ideas on organisation of the programme, e.g. distance learning facilities, flexibility, on-the-job training, to maximise existing resources

		• Proposed time lines for program set-up • Promotion of the programme to relevant potential participants. • A set of success criteria and evaluation of the courses • Process and criteria for half-way evaluation • Outline of the structure and viability/solidity of the Applicant Consortium
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 2.0 million for this project.

16. Pharmaceutical Medicine Training Programme

0	Topic Code	IMI_Call_2008_1_16
1	Topic title	IMI Pharmaceutical Medicine Training Programme
2	Project description	The industry has a need for professionals with a comprehensive overview of the medicines development process. This especially required at a managerial level, both for line managers and project managers at all stages of the process who are involved in portfolio decisions. Further scientists working in SMEs often come from academia and have little knowledge of the complexity and requirements for developing medicines and need therefore this comprehensive overview. The result will be improving professional effectiveness by promoting education and training in Pharmaceutical Medicine throughout the European Union in order to address the present needs and future competitive demands of highly qualified professionals (physicians and other life science graduates) in this key area of expertise. This is to be accomplished by the harmonised activity of existing and new courses in pharmaceutical medicine. Pharmaceutical Medicine (PM) is a medical scientific discipline concerned with the discovery, development, evaluation, registration, monitoring and medical aspects of marketing of medicines for the benefit of patients and the public health. PM is an interdisciplinary field. Although the role of physicians is necessary, important and not interchangeable, many other professionals with different life sciences background (Pharmacy, Biological and Health Sciences, etc.) currently practice in this area of expertise in the pharmaceutical industry and allied industries (e.g. CROs), regulatory bodies and other institutions. Education and training (E&T) in PM has been of paramount importance to ensure professional competence and enhance the value of the PM specialist. Currently a number of post-graduate courses in PM exist around Europe. Many of these courses were established by the national associations of PM in collaboration with local universities (see www.ifapp.org). E&T in PM is also provided in Europe as in-house activities in many pharmaceutical companies, and commercial and non-commercial providers offer courses of various contents and duration. Although these are valuable activities, they cannot be considered as comprehensive, structured, widely available and quality assessed educational activities as the courses mentioned before. To address this, a comprehensive and well structured IMI training programme at Masters level should be developed. The project comprises 2 phases: Phase 1, Analysis and establishment of the training

		programme, 1 year Phase 2, Deliver the training programme, 4 years Halfway through the 5 years programme, the IMI training programme must be evaluated to ensure satisfaction from course participants, industry and other users of the programme **Phase 1 Designing the best E&T product** Mapping and producing an inventory of existing courses. Defining E&T needs (for the industry, regulatory agencies, students, etc.) for Europe (various regions). Review of educational programmes and resources matched according to needs. Design of the programme, at various levels (foundation, advanced, high, Continuing Medical Education/Continuing Professional Development, CME/CPD): contents, delivery, tuition, assessment, collaboration with industry and other parties (Regulatory Authorities). The principles ruling this initial process are building on existing practice, flexibility (modular approach), efficiency of the use of resources, harmonisation, transportability of credits and a pan-European scope following Bologna criteria for European Higher Education Area. Also important is the integration of this project with other in-parallel E&T initiatives for other professionals (pre-clinical medicines development, safety science, etc.) to allow for transdisciplinary cross-fertilisation and enlarging the scope of applicability of the various programmes. Quality in the whole process is to be ingrained in all aspects of the programme developed, from content to implementation and assessment. Rating high among the priorities of this initial phase will be setting up quality criteria for all activities and aiming for a high quality content of the training programme, to be completed with appropriate assessment resulting in a diploma and should be developed for recognition on a Master's level of Advanced Studies in Drug Development Sciences **Phase 2:** Implementing the best E&T solution through a European network of E&T elements: existing and new courses, other outreach facilities and collaboration with pharmaceutical industry and regulatory agencies. • The programme should comprise the equivalent to the workload of a full-time student during one academic year; however it should be possible to enlist on a part time basis to complete the programme within 2 to 3 years The programme should cover the following needs: • Basic training in PM at the postgraduate level • Advanced education and practical training • Elective courses/programmes in areas requiring

		particular expertise • Comprehensive high-quality programme (Masters level) • Specific E&T initiatives for other professionals involved in activities governed by Pharmaceutical Medicine (e.g. GCP for research teams in drug clinical trials) The project aims to significantly expand the number of participants in E&T in the various activities by reaching persons currently experiencing difficulties in access (e.g. those located in Central and Eastern Europe). Improvement in quality, providing the best fit to needs and continuous improvement, will also rate high in the implementation phase. Finally, the implementation activities will provide a basis for establishing PM as a separate medical specialty throughout Europe.
3	Key deliverables of the project	• A Coordinating Board, comprised of members belonging to the various stakeholders of E&T in Pharmaceutical Medicine in Europe, ensuring the external validity and practical application of the proposals, as well as the adequacy of contents and solutions proposed • Map of existing E&T training resources in Europe • Analysis of E&T needs in PM in Europe. Matching with existing resources. Gap-analysis and plans to solve any discrepancies. • A description of the most adequate educational programmes and training schemes at foundation, advanced, and elective levels, high qualification (Master's level) and CME/CPD • Harmonised contents (standard syllabus - modules) and suitable educational methods. Adequate and validated assessment methods. • Definition of adequate E&T requirements in PM, at the various levels, in relation to specialist recognition status in Europe • Pool of resources: teachers and materials. Quality management of these. Accreditation criteria and implementation. • Outreach (e-learning) programmes, methods and materials • Criteria for selection and assessment of training positions within the pharmaceutical industry, regulatory authority and others • Quality management criteria and guide for implementation. Accreditation process and implementation. • A network of established university post-graduate

		courses in PM delivering programmes in a harmonised fashion, using similar educational and assessment methods and employing accepted quality management methods to include accreditation. • Stimulating the participation of centers in all parts of the EU • Organization of advanced workshops. The scientific organization (choice of topics and speakers) will be provided centrally. The workshops will be organized in different European cities with rotation from one year to the next. Topics may include: optimisation of early drug development, novelties in clinical trials, current issues in bioethics and evolution of the pharmaceutical market. These advanced workshops are intended for course participants to complement basic modules as well as for the CPD of recognized pharmaceutical physicians. • E-learning tool for training clinical investigators: A course will be developed complying with the syllabus published by the European Science Foundation in 2001 with a focus on GCP and containing chapters on the design of clinical trials, the ethical and regulatory aspects, the organization and conduct of clinical trials and data analysis and publication. This course will be made available to the European medical and paramedical community. • The programme will be evaluated based on the number of course participants and the number of employees recruited from non-EFPIA course participants.
4	EFPIA participants in the project	Almirall, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Chiesi, Eli Lilly, Esteve, Genzyme, GSK, Johnson & Johnson, Lundbeck, Merck, Merck Serono, Novartis, Novo Nordisk, Orion, Pierre Fabre, Pfizer, Roche, Sanofi Aventis, Servier, Sigma-Tau, UCB.
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Promotion of E&T in PM among their employees by allowing them to devote time off work to undertake the appropriate programmes. • Payment of the tuition fees of the courses for employees. • Senior members of their staff time off work to serve as educators or assessors of the proposed educational programmes. • Sharing of resources of their existing in-house training programmes with a “common house” of educational materials and personnel in Pharmaceutical Medicine. • Facilitation of training in Pharmaceutical Medicine by creating/maintaining recognised “training positions” in their own structures with adequate support of in-house

		mentors. • Input to members of the consortium on new scientific ideas and technologies
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 4 million covering 50 EFPIA employees participating in course and senior staff members as members of faculty over the 4 year period • Cost of EFPIA employees' participation in project and courses' development • Senior staff members to be members of faculty for lecturing and as assessors • Preparation of lectures • Travelling and accommodation in connection with lectures • Development of study cases • Sharing existing relevant in-house training programmes and/or educational materials • Facilitation of training by creating/maintaining recognised "training positions" in the companies with adequate support of "in-house" mentors • Hosting course/modules, lecture rooms and facilities
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Outline of the structure and viability/solidity of the Applicant Consortium • Plan to design and implement the programme • Description of the content of the course modules and requisites for quality assurance measures • Considerations on opportunities to establish an European accreditation of such programme • Innovative, realistic ideas to be built in the proposed programme, e.g. distance learning facilities, flexibility, on-the-job training, to maximise existing resources • Proposed time lines for program set-up • Promotion of the programme to the relevant potential partners • A set of success criteria and evaluation of the courses • Process and criteria for half-way evaluation
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 3.0 million for this project.

17. Integrated Medicines Development Programme

0	Topic Code	IMI_Call_2008_1_17
1	Topic title	IMI Integrated Medicines Development Course Programme for non-specialists
2	Project description	Many of the stakeholders who are indirectly involved in the medicines development process or parts of this are asking for knowledge about this complex process. 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 stakeholders who are involved to greater or lesser extents in the process of medicines development. Examples are: journalists, patient organisations, 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 stakeholders more directly involved, e.g. SME personnel, project managers, general mangers etcetera. To address this, a modular course to provide an overview of the medicines development process including regulatory, health economics and ethics requirements should be developed. The course is intended to provide an overview for people who are not directly involved in the research. Specific modules should be directed towards members of ethics committees and patient organisations. The effect of this programme will be more qualified input from stakeholders in the process and better decision making within the stakeholder organisations. The project comprises 2 phases: Phase 1, Establishment of the course programme, 1 year Phase 2, Deliver the course programme, 4 years Halfway through the 5 years programme, the IMI course programme must be evaluated to ensure satisfaction from course participants, industry and other users of the programme The programme could comprise 2 tracks: • A short track (approximately one week duration, summer school format) to train journalists, patient organisations, ethics committees, venture capitalists,

		etcetera who need a very brief overview of drug development. • A longer track (modular concept, over about 6 months, e.g. lectures/workshops over a couple of days once or twice monthly) for stakeholders from various backgrounds: basic biology, toxicology, clinical research, regulators, managers, who need more in depth knowledge to give them a, 'helicopter view' of drug development. For both tracks, mixing participants from different skills/background in the same courses would add value through enhancing interdisciplinary interaction. Furthermore, the faculty of the courses should reflect this as well. The modules could be: • Target identification: basic molecular and cell biology and biochemistry, 'omics', high throughput technology, systems biology, bioinformatics and in silico models • Target validation: in vitro and in vivo models, imaging and biomarker identification • Toxicity - safety - pharmacovigilance- risk management and communication of benefit-risk • Basic clinical pharmacology, translational medicine • Clinical trials in the EU including critical differences to other regions of the world (a short version of this module could also be used for investigator training for pan-EU trials, over one or two weeks). • study design, methodology phase 1 to 4 (including innovative designs), validation and use of biomarkers, systematic reviews, meta-analyses • data management, biostatistics • roles and responsibilities, cost • recruitment and investigation of patients • ethics, regulatory affairs, insurance, adverse event evaluation and reporting • conduct and monitoring of the study, GCP, quality assurance • Legal, regulatory framework, intellectual property • Health economics, outcomes, drug market and financial aspects of drug life cycle
3	Key deliverables of the project	• Evaluation of the utility of having a short and a long track versus having one course following the long track outline above starting with an introduction in the form of an overview satisfying the needs for the short course.

		• A programme for the course • A European Network of Faculties (universities and private institutions) • More than 100 participants completed the course • Administration of courses • The programme will be evaluated based on the number of course participants and the course participants utility of the courses
4	EFPIA participants in the project	Almirall, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Chiesi, Eli Lilly, Esteve, Genzyme, GSK, Johnson & Johnson, Lundbeck, Merck, Merck Serono, Novartis, Novo Nordisk, Orion, Pierre Fabre, Pfizer, Roche, Sanofi Aventis, Servier, Sigma-Tau, UCB.
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Input to course content • Lecturers for the courses • In house mentors for the companies' students • Provision of case studies and material from in house courses and presentations • Provision of short term tutoring programmes in an industry environment • Provide input on new scientific ideas and technologies
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 3 million covering 25 EFPIA employees and senior staff members as members of faculty over the 5 year period. • Cost of EFPIA employees' participation in course development • Senior staff members to be members of faculty for lecturing and as assessors • Preparation for lectures • Travelling and accommodation in connection with lectures • Development of case studies • Sharing existing relevant in-house training programmes and/or educational materials • Hosting courses/modules, lecture rooms & facilities • Paying course fees and expenses of employees participating in programme.

8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • Outline of the structure and viability/solidity of the Applicant Consortium • Plan to set up and deliver the programme • Description of the content of the course modules and requisites for quality assurance measures • Innovative, realistic ideas on organisation of the programme, e.g. distance learning facilities, flexibility, on-the-job training • Proposed time lines for programme set-up • Specification of relevance to the various stakeholders • Promotion of the programme to relevant potential participants • A set of success criteria and evaluation of the courses • Process and criteria for half-way evaluation
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 2.0 million for this project.

18. Pharmacovigilance Training Programme

0	Topic Code	IMI_Call_2008_1_18
1	Topic title	IMI Pharmacovigilance Training Programme
2	Project description	Pharmacovigilance is a pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects of medicines. 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, both in clinical trials as well as the general practice and hospital settings. 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, thus a PhD programme is proposed to develop these. To address this, pharmacovigilance training and research at 3 levels are needed: 1. A Short overview course on risk communication for journalists, venture capitalists, patient organisations, health care providers, etc. who need an introduction to pharmacovigilance, including its strengths and weaknesses. This will include an understanding of the different measures of risk and the factors that may confound their interpretation, of the inherent risks associated with a disease and of the beneficial and undesirable effects of medicines, 2. A training programme at Masters level focussing on the methodologies and tools used in contemporary pharmacovigilance should be developed to train professionals in industry and regulatory agencies who hold a degree in life sciences, 3. A long term programme (ex: PhD) to identify current gaps, and assess and develop methods for benefit-risk communication. The research will be used to develop best practices and principles to improve upon existing methods and tools used for communication. The project comprises 2 phases: Phase 1, Establishment of the training programme, 1 year

		Phase 2, Deliver the training programme, 4 years Halfway through the 5 years programme, the IMI training programme must be evaluated to ensure satisfaction from course participants, industry and other users of the programme. The programme should utilise established courses providing the necessary content and new courses developed by the consortium, The programme should be open to scientists working in industry, academia or regulatory agencies and the short course should be open to all stakeholders, Faculty should consist of teachers from academia/industry/regulatory agencies The programme should be modular to ensure flexibility and to cope with future scientific development, The programmes should include a combination of lectures and workshops and should enable distance learning assuming that participants continue their normal work, Each topic to be completed with an assignment related to a concrete safety issue (e.g. a case from the student's institution), The programme should comprise the equivalent to the workload of a full-time student during one academic year, however it should be possible to enlist on a part time basis to complete the programme within 2 to 3 years, There should be an option for scientists to pursue or complete single topics / modules (continuing professional development). **The Master's level programme** The following list of topics to be addressed is intended to set the scope for the programme, not to set limitations for the innovative thinking of the consortium. The topics of the IMI training programme should address: Pharmacovigilance, including • General principles of assessing drug safety in all phases, Classification of adverse drug reactions, Causality assessment, notification systems, Eudravigilance, Roles and responsibilities of the Qualified Person in Pharmacovigilance, Regulatory environment And relevant specific topics. Advanced pharmacoepidemiology, including • Objectives, definitions and principles of pharmacoepidemiology, measurement, data sources, incidence, risk measures, statistical analysis, study designs, regulatory aspects and conduct of pharmacoepidemiological studies.

		Databases & electronic registries for drug safety, including • Technical aspects, types of databases, data requirements for drug safety and retrospective studies, MEdDRA and other terminologies, Major EU databases, statistical analyses, study designs and data analyses. Risk management, including risk minimisation • Principles of risk management, ICH E2E pharmacovigilance planning, EU Risk Management Plan,Risk minimisation and management. Benefit -risk communication • Benefit-risk assessment, Perceptions of risks and benefits, communication including technical aspects and channels: characteristics and effectiveness depending on target audience (patients, HCP, media, public health authorities, etc) **The Long term programme** The long term programme should conduct research to identify current gaps, and assess and develop best practices for benefit-risk communication from industry and regulatory agencies to healthcare professionals, patient organistions and other stakeholders (e.g. payers, the media, etc.). The programme will address methods for delivering concise, evidence-based and understandable information. The research activity shall include testing of the effectiveness of current communication tools, review of published literature related to communication of risks, assessment of the impact of current communications, and consultation with experts in the areas of public communication and social science as well as the involvement of patient organisations in benefit-risk assessment. The project could be approached in several phases, with the initial phase focussing on selection of communication tools to be evaluated in the project.
3	Key deliverables of the project	Short overview course for non-scientific audience • A programme for the course, • The course will be evaluated based on the number of course participants and the course participants utility of the courses. Training programme on contemporary pharmacovigilance for professionals • A programme for multidisciplinary training of scientists involved in pharmacovigilance, • A European Network of Faculties (universities and private institutions), • Establishment of programme, • More than 50 participants in programme with at least 20 completed full programme,

		• Explore possibilities to come up with pan European criteria to ensure consistency of the training efforts in the field of science graduate of the pharmaceutical industry • The programme will be evaluated based on the number of course participants and the number of employees recruited from non-EFPIA course participants.
4	EFPIA participants in the project	Almirall, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Chiesi, Eli Lilly, Esteve, Genzyme, GSK, Johnson & Johnson, Lundbeck, Merck, Merck Serono, Novartis, Novo Nordisk, Orion, Pierre Fabre, Pfizer, Roche, Sanofi Aventis, Servier, Sigma-Tau, UCB.
5	Role of EFPIA participants in the project	The EFPIA participants will contribute: • Input to industry need for course content • Lecturers for the courses • In house mentors for the companies' students • Provision of case studies • Provision of short term tutoring programmes in an industry environment • Industrial supervisor for PhD fellow(s) • Provide input to members of the consortium on new scientific ideas and technologies
6	Indicative duration of the project	5 years
7	Indicative total in kind contribution from the EFPIA companies	€ 3.5 million covering 35 EFPIA employees and senior staff members as members of faculty over the 5 year period and 2 PhD fellows • Cost of EFPIA employees' participation in course development • Senior staff members to be members of faculty for lecturing and as assessors • Preparation for lectures • Travelling and accommodation in connection with lectures • Development of case studies • Sharing of existing relevant in-house training programmes and/or educational materials • Hosting of courses/modules, lecture rooms & facilities • 50% of the standard PhD salary • Industry bench costs, i.e. location, use of apparatus etc. • Administration of salary, employment contract etc • Industry supervisor

8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	The contribution from the Applicant Consortium is expected to include all aspects of the following areas: • The programme should be developed by a consortium of experienced academic course providers with a proven record. The consortium may include commercial course providers, • Outline of the structure and viability/solidity of the Applicant Consortium • Plan to set up and deliver the programme • Description of the content of the course modules and requisites for quality assurance measures • Innovative, realistic ideas on organisation of the programme, e.g. distance learning facilities, flexibility, on-the-job training, to maximise existing resources • Proposed time lines for programme set-up • Promotion of the programme to relevant potential participants • A set of success criteria and evaluation of the courses • Process and criteria for half-way evaluation
9	Indicative financial support from IMI JU to the "Applicant Consortium"	The IMI JU financial contribution to the "Applicant Consortium" is expected to be in the region of € 3.0 million for this project.