Innovative Medicines Initiative

The Innovative Medicines Initiative (IMI)
Scientific Research Agenda
Revision 2011

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1 Foreword

The mission of the Innovative Medicines Initiative (IMI) is to contribute to creating biomedical research and development (R&D) leadership for Europe to benefit patients and society. To this end the two key aims of IMI are to support the faster discovery and development of better medicines for patients and to enhance Europe's competitiveness. IMI will implement innovative Patient Centred Projects that address the principle causes of delay (bottlenecks) in the current biomedical R&D process.

The IMI Scientific Research Agenda (SRA) includes recommendations to address such bottlenecks and is at the same time the instrument to guide the implementation of IMI projects. The SRA was conceived as a 'living' document to be up-dated based on scientific advances and the evolution of industry. The original SRA was released in March 2008 and represented the outcome of an extensive consultation between Europe's key stakeholders in the biomedical sector. From 2008 there has been major progress in research and technology with implications for drug R&D, and significant changes in the pharmaceutical industry and in the overall healthcare landscape. For these reasons both founding members agreed that the SRA should be updated and revised ahead of the 4th IMI Call for Proposals. The revision has been led by the IMI Scientific Committee (SC). Major feedback from participants in the revision of the SRA was, that in order to make a real difference to European global competitiveness, IMI should consider focusing overarching strategic initiatives on 'game-changing' ideas and areas where the maximum number of companies can join forces. From this, the concept of the 'Think big' projects developed which are strategic themes under which future projects will be developed, that will change the landscape in which pharmaceutical industry, academic institutions and healthcare operate.

'Safety sciences', 'Research on metabolic diseases', 'Knowledge management', 'CNS disorders' and other themes define already existing IMI Research Priorities with critical mass. In the course of the revision process important new Research Priorities have been identified which might constitute Research Priorities for the coming Calls, together with some of the original ones. The research priorities, which have been proposed are listed and presented together with potential Call topics.

2 Introduction

2.1 The process for the revision of the Scientific Research Agenda

The SRA revision process was initiated in 2010 when the Scientific Committee produced a Status Report, 'Trends, Challenges and Opportunities in Drug Research' providing an overview of what they see as innovative research opportunities existing in the academic/SME (Small Medium Enterprises) world.

Following on from the Status Report, the IMI Executive Office and the Scientific Committee organised a workshop (June 1-2, 2010) to solicit ideas and feedback from stakeholders including industry, academia, regulatory authorities and patient organisations. During the IMI Stakeholder Forum (22 June 2010) further input was solicited from the stakeholders. During the summer of 2010, feedback and comments on the Scientific Committee's Status Report were provided by the EFPIA Research Directors Group (EFPIA RDG) and proposals for the future strategic research themes (Think Big') were given.

For Knowledge Management (KM), a workshop report was produced. Following this workshop report, a proposal was made to the EFPIA RDG proposing the establishment of:-

a) An IMI KM Service Delivery Group with members from EFPIA, IMI JU office and academia, to support IMI JU office in the execution of a KM service infrastructure. This group involves representatives from all ongoing efficacy, safety and KM projects to ensure co-ordination, sharing best practice and defining standards for all calls having a KM component;

b) A KM Affinity Group lead by senior EFPIA KM experts to define industry's over-all ambition and strategy for informatics systems, components, services and standards needed to enable collaborative drug discovery and development.

The status of the revision was presented to the members of the States Representative Group (SRG) in a Meeting on 20 January, 2011 and their input was solicited. By end of February the Scientific Committee had submitted its proposal for the revised SRA including the input from the SRG. The Executive Office assisted the Scientific Committee in preparing a draft that was sent Mid-March 2011 for consultation to the EFPIA Research Directors Group, the European Commission and the States Representatives Group. The present final version of the SRA represents the consolidated output of the whole process.

2.2 Reasons for a revision of the Scientific Research Agenda

Since the drafting of the original SRA, the drug development industry is facing growing external pressures from the drive for personalised medicine, pricing pressure, demographic shifts and consumerism, all of which create new challenges but also opportunities. A fundamental change in the health care 'ecosystem' is starting to play itself out, as pointed out by the recent Ernst & Young Global Pharmaceutical Industry Reports for 2010 and 2011[1]. On one hand, new transformative trends, such as health care reform and health IT, are driving the system to include many partners not traditionally involved in the health care business. On the other, where patients have traditionally been relatively passive participants in health delivery, they are now being empowered by technological progress (such as internet, smart phones) to become educated 'super-consumers' with a much more active role in management of their health care. Furthermore, the socio-economic background for research has changed due to the financial crisis of 2008. The funding of the biotech industry is fundamentally challenged by very limited availability of 'risk investment money'.

In this scenario the IMI Scientific Committee underlines several reasons for the revision of the SRA:

- Science and technology have moved on rapidly in the last five years and it is necessary that this progress is reflected and integrated in the IMI Programme, and that engagement of the Scientific Community is boosted.
- While much progress has been fostered by the first wave of IMI projects and other ongoing initiatives to address many of the bottlenecks outlined in the original SRA, there is still a need to continue to improve the understanding of underlying disease mechanisms, to develop and validate tools to better inform target and patient selection and to effectively deliver drugs.
- In response to the above mentioned pressures the Scientific Community as a whole is recognising the need for pooling and sharing data, knowledge, and expertise for the development of better tools and methods required to progress the next generation of innovative medicines.

This 'pre-competitive research' concept is at the core of IMI, and the novel joint ventures that IMI supports and manages have the potential to deliver huge benefits for the pharmaceutical industry and society in Europe at large.

All the described changes and transformations have created additional knowledge gaps and bottlenecks, which had not been addressed in the original IMI SRA. Furthermore, the first three IMI Calls have already addressed a number of the priorities within the original SRA as indicated in Tables 1 & 2. Important 'Lessons learned' can be extracted from the first three calls and used to ensure the maximal impact of research conducted under IMI through implementation of the new 'Think Big' themes.

This document brings together the learning experiences from the previous Calls along with the consolidated input of the IMI stakeholders and proposes the areas that the Innovative Medicines Initiative should support as it moves forward.

[1] Ernst & Young (2010) Global pharmaceutical industry report 2010, Progressions Pharma 3.0, and Ernst & Young (2011) Global pharmaceutical industry report 2011 Progressions Building Pharma 3.0

Table 1. Overview of projects of 1st IMI Call

CALL	TITLE OF PROJECT	AREA	OBJECTIVE
1st Call	SAFE-T	Safety	Identification of sensitive and predictive biomarkers of liver, kidney and vascular system damages for use in clinical drug development
1st Call	PROTECT	Safety, Pharmacovigilance	Enhancement of safety monitoring through new tools and methodologies to evaluate risk-benefit profiles of drugs
1st Call	SUMMIT	Efficacy, Metabolic Disorders, Diabetes	Identification of biomarkers to identify diabetic patients at high-risk for cardiovascular complications in diabetes
1st Call	PHARMACOG	Efficacy, Brain disorders, Alzheimer's Disease	Development and validation of new tools for testing of candidate drugs to treat Alzheimer's Disease
1st Call	IMIDIA	Efficacy, Metabolic Disorders, Diabetes	Generation of novel tools, biomarkers and fundamental knowledge on beta-cells to improve diabetes care
1st Call	NEWMEDS	Efficacy, Brain disorders, Schizophrenia & Depression	Development of biomarkers, tools and models to allow more targeted treatments for schizophrenia and depression
1st Call	U-BIOPRED	Efficacy, Respiratory Disorders	Development and validation of a biomarker 'handprint' in asthma to predict disease severity and allow more personalised therapies
1st Call	EUROPAIN	Efficacy, Brain disorders, Pain	Better understanding of chronic pain mechanisms to aid the development of novel drugs
1st Call	PROACTIVE	Efficacy, Respiratory Disorders	Production of validated patient reported outcome questionnaires to measure physical activity in COPD as a research instrument
1st Call	MARCAR	Safety, non-genotoxic carcinogenesis	Identification of new biomarkers for drug-induced tumour formation
1st Call	E-TOX	Safety, knowledge management	Development of novel strategies and software tools for better prediction of drug side-effects
1st Call	EMTRAIN	Education & Training	Establishment of an European platform for higher education/training on the lifecycle of medicines
1st Call	EU2P	Education & Training	Establishment of an European platform for education and training in pharmacovigilance and pharmacoepidemiology
1st Call	PHARMATRAIN	Education & Training	Establishment of an European masters program on pharmaceutical medicine and drug-development sciences
1st Call	SAFESCIMET	Education & Training	Establishment of an European education and training program in safety sciences for medicine

Table 2. Overview of projects of 2nd IMI Call

CALL	TITLE OF PROJECT	AREA	OBJECTIVE
2nd Call	BTCURE	Efficacy, Inflammatory Disorders	Development of future curative treatments for early intervention against rheumatoid arthritis
2nd Call	ONCOTRACK	Efficacy, Cancer	Identification of new models to predict effects and side effects of cancer treatments in defined groups of patients
2nd Call	DDMORE	Knowledge Management	Establishment of standards for common tools to enhance modelling and simulation technologies
2nd Call	PREDECT	Efficacy, Cancer	Development of new models for novel treatments of breast, prostate and lung cancer
2nd Call	QUIC-CONCEPT	Efficacy, Cancer	Standardization and qualification of imaging biomarkers for phase 1 oncology clinical drug development
2nd Call	RAPP-ID	Efficacy, Infectious diseases	Development of a point-of-care test for rapid detection of microbes
2nd Call	OPEN-PHACTS	Knowledge management	Development of an open access innovation platform dedicated to drug discovery using a semantic web approach
2nd Call	EHR4CR	Knowledge management	Development of a electronic health records platform to support R&D projects on innovative medicines

Table 3. Call Topics of 3rd IMI Call

TITLE OF TOPIC	AREA	OBJECTIVE
Improving the Early Prediction of Drug Induced Liver Injury in Man	Safety	Identification of new assays and models, which can be used during drug discovery and early non-clinical development to support design, ranking and selection of drugable candidates that have low propensity to cause DILI in man
Immunogenicity: Assessing the Clinical Relevance and Risk Minimization of Antibodies to Biopharmaceuticals	Safety	Investigation of the clinical relevance of biopharmaceutical-associated immunogenicity in order to increase patient safety, and optimize drug development
Improving the Preclinical Models and Tools for Tuberculosis Medicines Research	Efficacy, Infectious diseases	Development of an integrated set of pre-clinical in vitro and in vivo models that provide critical data to design optimized clinical studies in TB patients.
Immunosafety of Vaccines – New Biomarkers Associated with Adverse Events (Early Inflammation, Autoimmune Diseases and Allergy)	Safety	The characterization of early inflammation induced by vaccines currently on the market and the identification and validation of biomarkers of early inflammation and allergic responses The identification and validation of early biomarkers of autoimmunity and their use to help identifying population at risk of developing autoimmunity The analysis of the incidence and epidemiology of autoimmune disease in the general population and the link to genetic background or previous events in the life of patients
Translational Endpoints in Autism	Efficacy, Brain disorders, Autism	Development and validation of translational approaches for the advancement of novel therapies to treat ASD Setting of new standards in research and clinical development to aid the drug discovery process Identification and development of expert clinical sites across Europe to run clinical studies and trials and so create an interactive platform for ASD professionals and patients
Development of Personalized Medicine approaches in Diabetes	Efficacy, Metabolic disorders, Diabetes	Development of robust disease stratification and response tools to overcome current bottlenecks in drug development for diabetes and to improve patient care through a personalized / stratified therapeutic strategy
Fostering Patient Awareness on Pharmaceutical Innovation	Education & Training	Improving the understanding of pharmaceutical research and development among patients, carers and other interested lay people across the European Union

3 The IMI Research Architecture - Defining the Framework

3.1 Bottlenecks

The key aim of IMI is to address bottlenecks in pharmaceutical R&D leading to faster discovery and development of better medicines for patients and the enhancement of Europe's competitiveness.

In the steps from one phase of the drug development process to the next – as outlined in the matrix of the original SRA - bottlenecks often appear. However, bottlenecks not only arise during translational steps, but are intrinsic to many phases of drug research, both during discovery and development. Examples are lack of understanding of disease aetiology, lack of validity of new tools to support effective translation of pharmacology from animal models to the clinic and to support key decision-making early in the drug discovery process. This is now considered in the revised SRA proposed by the IMI Scientific Committee. As described in the introductory section there has been major progress in science and significant changes and transformations in the pharmaceutical industry and the healthcare system at large. These events create unique opportunities for the future of drug R&D, but also shine light on additional knowledge gaps and bottlenecks, which had not been identified in the original IMI SRA and are considered in this updated version.

3.2 Pre-competitive Research and Collaborative Innovation

The concepts of pre-competitive research and collaborative innovation are key elements of the IMI framework. IMI-supported research in itself aims at being high quality, cutting-edge collaborative research in a unique setting with participation of both industrial and academic scientists, patient groups and scientific input from regulatory authorities. Pre-competitive research is capability driven and not product driven. Pre- or non-competitive activities are, from an industrial perspective, activities that do not lead directly to the approval of a medicine or a vaccine etc*. per se*, but develop the knowledge required to increase the efficiency of the drug discovery process. IMI provides a platform for these kinds of activities. It is a level playing field, where pharmaceutical industrial researchers, academic researchers and other stakeholders can best participate in research collaborations on an equal partnership level by making quantifiable contributions, and where several traditionally competing companies join forces. A key challenge for IMI is to continue to succeed in ensuring the engagement of the broadest range of stakeholders, including research intensive SMEs. A key objective of IMI is to

promote collaborative innovation fostering the cultural change necessary to create new ways of engaging collaboratively large and small companies, governments and academic institutions and of harnessing knowledge and capability residing both within and beyond organizational boundaries. The ongoing IMI projects are indeed showing the value of such an approach, and the facilitation of easy flow of knowledge across and within sectors will continue to be a key component of future IMI activities.

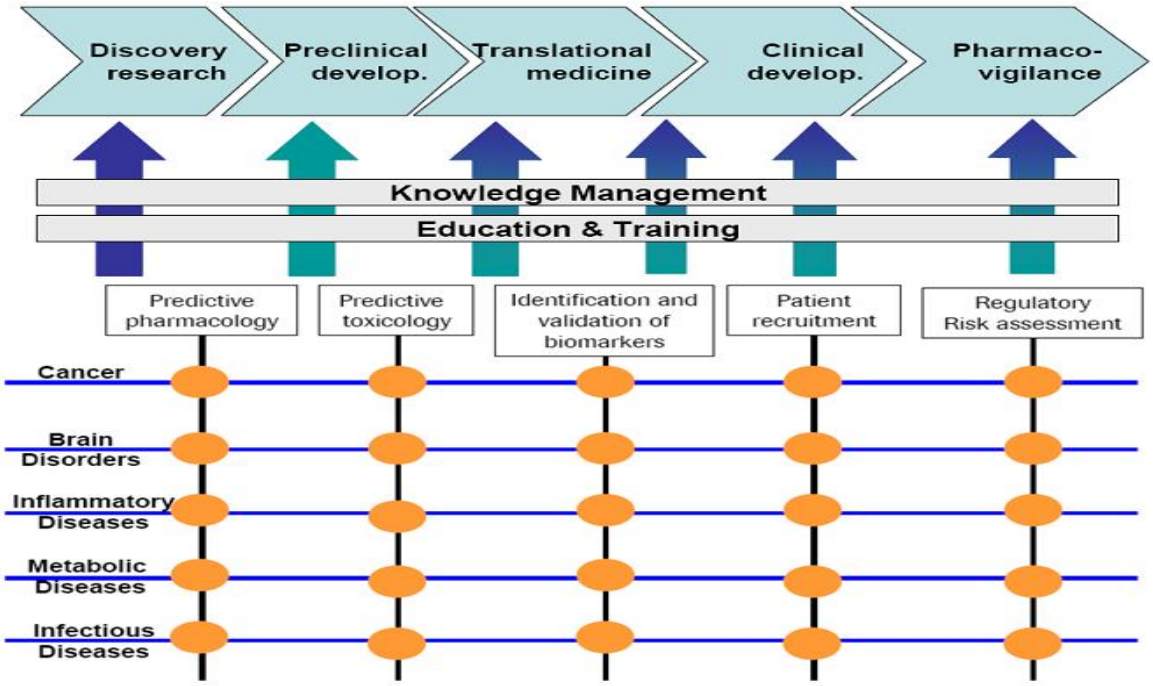
3.3 The IMI Areas of Research Interest

In the first SRA (2008) four research pillars were identified as Efficacy, Safety, Knowledge Management and Education & Training (Figure 1).

Figure 1: Four IMI Pillars of the 2008 Scientific Research Agenda

The strategy of the original SRA was then organized in a matrix (see Figure 2), where the themes 'predictive pharmacology', 'predictive toxicology', 'identification of biomarkers', 'patient recruitment', 'validation of biomarkers' and 'regulatory risk assessment' correlated to the 'R&D path' from 'discovery research' to 'pharmacovigilance' and made up the horizontal line of elements, while a group of 'selected diseases' constituted the vertical dimension. 'Education and Training' and 'Knowledge Management' represented further horizontal key Areas of Research Interest with implications to all steps of the R&D path.

Figure 2: IMI Research Matrix from the IMI Research Agenda 2008

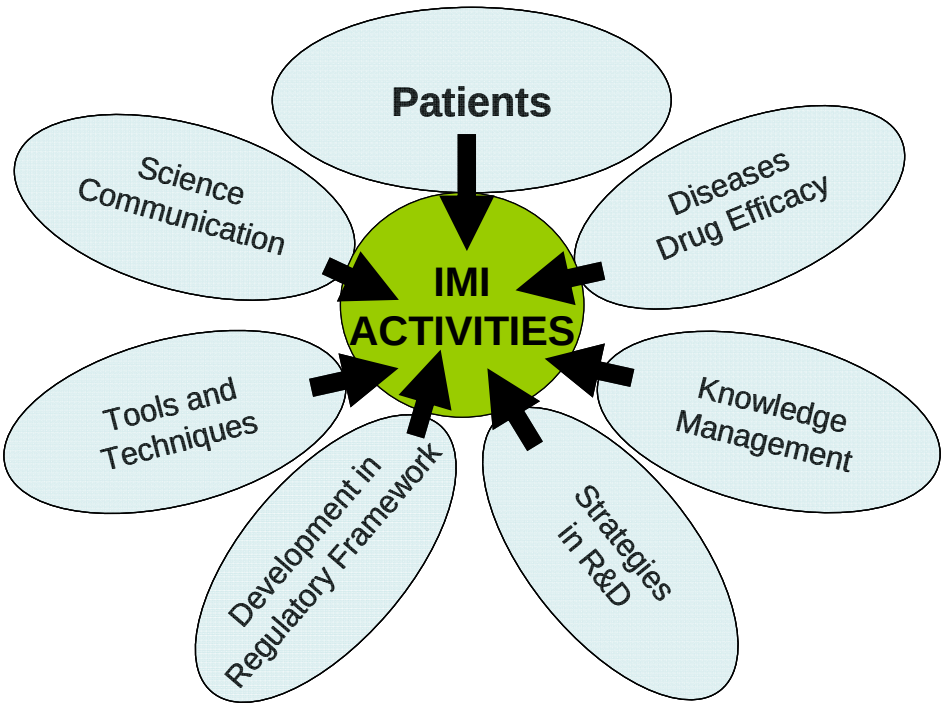


3.3.1 Replacement of the Research Pillars by 7 Areas of Research Interest

In light of the progress of science and technology made in recent years and of the changes in the pharmaceutical industry and health systems, the original IMI SRA research strategy defined along the lines of four separate 'Pillars' is now not comprehensive, nor focused enough.

In order to ensure that in the future, IMI activities will succeed in delivering projects of real strategic value to the biopharmaceutical community and European citizens, in this revision the 'Pillars' have been expanded to a system of 7 Areas of Research Interest (Figure 3). These Areas are highly interconnected and for most, a combination of bottlenecks that are relevant to more than one of them will need to be considered to ensure focus on key 'game-changing' initiatives. These areas cover most of the relevant aspects of drug research as follows.

Figure 3: Areas of Research Interest of the revised IMI SRA



3.3.2 The Patient in the Focus of Research

During the first half of the last century, the 'art of making drugs' (i. e. 'manufacturing drugs') was the dominant factor of drug research. In the second half of that century 'drug targets' – both on genotype and phenotype level – were in focus. Progress in the knowledge of disease aetiology and pharmacogenomics will support the development of more efficacious stratified and individualised therapies. Progress in information technologies will enable outcomes that are of the highest importance to patients to be captured and processed much more efficiently, especially following registration of new medicines. Along with this hope for improved therapeutic success, and in light of the changes in the health care ecosystem as mentioned in the previous section, during the coming decade drug research will have to turn its attention increasingly towards the 'patient' as a data-empowered and educated 'super-consumer'.

From their early start, drug research programmes always need to be clearly focussed on the needs of the patient. Recent advances in technology allowing the collection of data directly from patients regarding drug effectiveness and safety will enable the

development of more targeted outcome measures for many diseases, where currently available regulatory approved clinical outcomes fail to have the sophistication and sensitivity to capture the full benefit of new therapies for the patients. This not only enables the patient to have a more influential role in the whole drug discovery process, but will improve the quality of data used to drive registration studies and lead to substantial improvement of the disease burden and positive health-economic effects for society. IMI research is 'patient-centric' and IMI provides, and will continue to do so, a valuable opportunity for patient groups to participate in applicant consortia and to influence the development of new partnerships that could address current bottlenecks in pharmaceutical R&D.

3.3.3 Diseases – Drug Efficacy

In the context of the changes faced by the pharmaceutical industries and the demand of the evolving health care ecosystem for not only demonstrating measurable medical benefit but also positive health-economic effects, developing new methods for evaluating drug efficacy as well as developing new interventions with enhanced drug efficacy are areas with significant challenges. In addition to the focus on 'improved translation', as outlined in the original SRA, patient compliance and targeted delivery of therapies are just some examples where efforts for improvement would be highly welcomed. Furthermore, education and increased focus on the generation of observational data sets earlier in drug development to evaluate new therapies, for example using observational or pragmatic trial designs, would improve our ability to investigate more thoroughly the unmet need and potential benefit in different 'target' populations.

3.3.4 Knowledge and Knowledge Management

As outlined in the original SRA, knowledge management is an essential factor of the overall success of each individual IMI project and the initiative as a whole. Handling of data generated inside and outside of IMI projects is now already the fundamental task of the present IMI Knowledge Management Service Delivery Group. This group is focused on developing the KM infrastructure required to ensure the effective integration of data sets generated across IMI projects as well as externally. This will act to ensure that synergies between ongoing projects within and outside of IMI are maximised and therefore ensure that resources are used in the most efficient way.

Of utmost priority is to ensure continuity of the high standards seen to date about the generation, handling, storing and utilisation of generated data, all of which affect the quality of outcomes from the IMI research matrix. Integration of data in their context to

generate new knowledge, for example, in correlating *in vivo, in vitro* and *in silico* research, will continue to be a key aspect of many current and future IMI projects. In the future, IMI will also have a stronger focus on sharing of 'best practice' across all IMI projects and on ways for ensuring the sustainability of databases and bio-banks created by IMI projects.

3.3.5 Strategies

During the last decades the drug discovery process has been developed into a very technically-efficient, sophisticated series of steps; gene – target – hit – lead – preclinical drug candidate (PDC). The remaining very high attrition rate in the development process continues to highlight the need to better understand disease aetiology on molecular, cellular and the system levels to better support patient selection and also to develop tools to improve our ability to identify effective medicines while rejecting ineffective ones much earlier in the development process. Failure due to unpredicted safety signals also still remains an important area of focus. Continued activity in this area is required if the attrition rate is to be significantly reduced especially in highly complex diseases. As in the original SRA, these areas will remain of strategic importance for the revision of the SRA. Modern 'omics'-focussed research combined with systems biology will lead to a better understanding of disease aetiology and will open up new avenues of drug research. Harmonising reductionist, systemic and holistic approaches in drug research is a specific challenge that future IMI activities should tackle: e.g. addressing bottlenecks in signalling- and pathway-based target research, as well as in systems biology-based target research.

3.3.6 Beyond Drug Discovery: Drug Development and the Regulatory Framework

The drug R&D path is a documented process with clearly defined steps to achieve approval of a medicine by the regulatory authorities. Successful translation of promising results from drug discovery into marketed medicines requires efficient development and production processes. Significant bottlenecks are currently present at the level of several technological aspects of drug development (e.g. for development of drug combinations or for oral administration of macromolecules), which all are controlled by the regulatory system.

This means that specific attention will have to be paid to key 'rate limiting' elements of the development process. A consistent framework for the acceptance and qualification of novel tools and technologies for regulatory use is needed to facilitate innovative and efficient research and subsequent application of its results to drug development. In

future IMI activities, the regulatory aspects of the technology of drug development that constitute major bottlenecks should be addressed. This will also help to improve the competitive situation of Europe in comparison to other regions currently focussing more on drug manufacturing.

In this context, the discipline of pharmaceutical sciences is critical to the development of new medicines. Pharmaceutical science is multi-disciplinary by nature, crossing the boundaries between chemistry, pharmacy, engineering, biology and medicine. Pharmaceutical science is a key element in delivering quality medicinal products to patients. Many elements of pharmaceutical science impact directly on the quality, safety, efficacy and cost of the products, the attrition of potential drug candidates and the speed to the market place and as such the delivery of new medicines to the patient. The revised agenda addresses research relevant to bottlenecks in pharmaceutical sciences, such as chemical and formulation technology, with a specific attention to the regulatory context.

3.3.7 Tools and Techniques

Progress in science, in particular in the life sciences, has provided and will continue to provide new, sophisticated research tools and methods and a constantly evolving scientific environment. The identification and 'qualification' of new tools and techniques and their implementation as approved standards for efficient R&D processes (together with regulatory scientists) is a key goal of IMI.

3.3.8 Education and Training: Science Communication at various levels

This element means an expansion of the 'Training and Education' pillar in the previous SRA. It should include aspects like 'communication to the public'. A strong, 'state of the art' Education and Training programme will strengthen the position of the European scientific community in global drug research.

3.3.9 Strategic Themes for IMI Research

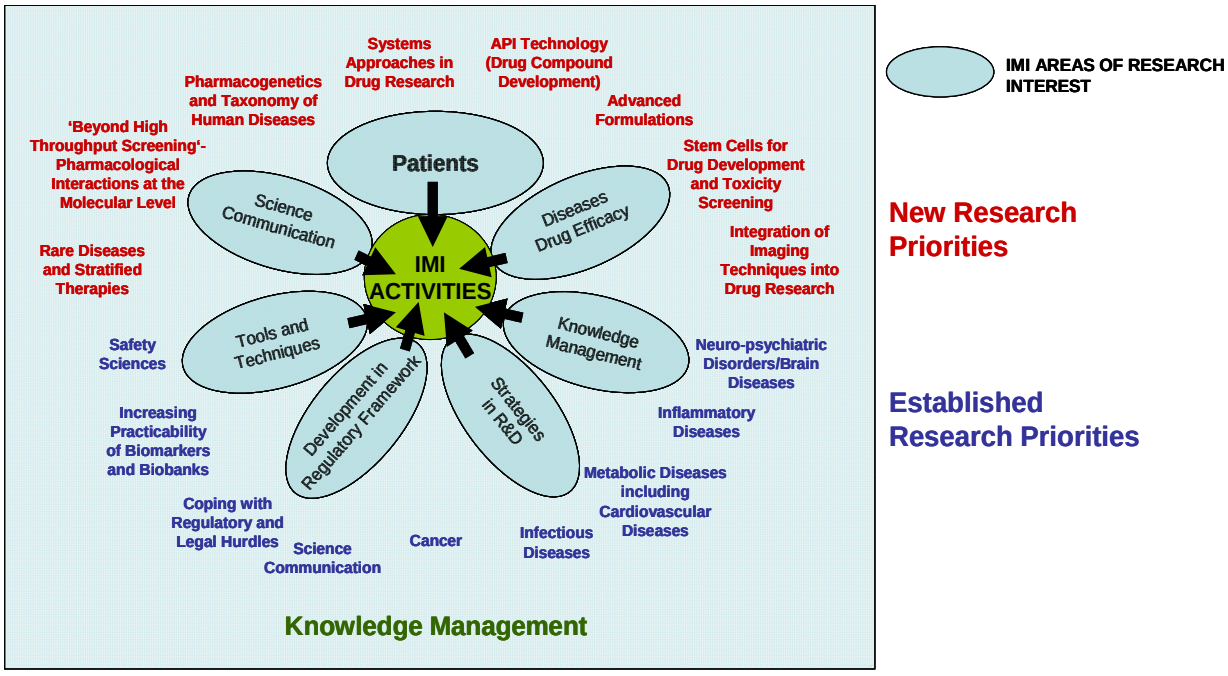
A major feedback from participants in the discussions regarding the revision of the SRA was that IMI should focus on defining strategic themes (initiatives), as research clusters focused on 'game-changing' ideas and areas where the maximum number of companies can join forces. 'Think big' priorities are to be defined as initiatives, which will change the landscape in which pharmaceutical industry, academic institutions and healthcare operates.

'Safety sciences', 'Research on metabolic diseases', 'Knowledge management', 'CNS disorders', and other themes made up the ten Established Key Research Priorities of the first phase of IMI and represent existing research clusters (see Tables listing ongoing IMI projects). These will be maintained in the revised SRA.

In addition, in the course of the SRA revision process, important new Research Priorities have been identified which have key strategic value for the future of pharmaceutical R&D.

According to their nature, such Research Priorities (new and established) may lead to projects, or project clusters, in only one or several Calls. Each of the following two sections describes respectively the entirely New Research Priorities, and the reassessed Established Research Priorities, listed with some indicative call topics. Each of them is correlated to at least one of the 7 new Areas of Research Interest, reflecting the need for strategically integrating many different aspects of science and technological investigation to achieve 'Think Big' objectives.

Figure 4: The Research Priorities in the Revised IMI Scientific Research Agenda



4 The 8 New Key Research Priorities

In order to successfully tackle the challenges and opportunities created by recent major progress in science, as well as the significant changes and transformations in the pharmaceutical industry and healthcare systems in general, IMI has to foster strategic initiatives focused on 'game-changing' ideas and areas where the maximum number of companies can join forces. Some of these areas had not been identified in the 2008 IMI SRA and are now included in the present revised SRA, as described below.

4.1 Pharmacogenetics and Taxonomy of Human Diseases

(Areas of Interests: Patient, Diseases, Knowledge)

The origin of the current classification of diseases dates back to William Farr's work in 1855. A major part of the criteria are based on anatomical foci of the disease, symptomatologic and epidemic patterns of the disease and very little, if any, are based on molecular findings which link more closely to effects of medicines. Major issues with this current taxonomy are that the criteria are based on secondary effects of the disease and thereby lack specificity. As a results of this, several disease entities overlap, the identification of specific and objective diagnostic criteria are hampered, and consequently, the development of more molecularly directed and thereby more effective medicines is delayed.

Pharmacogenetics has opened the door to individualised therapies. Furthermore, recent progress in epigenetics (heritable changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence) has generated huge interest in the role of epigenetic changes in disease biology.

The oligo- or multigenetic origin of many diseases is, at the same time, a chance for new therapies and a challenge to obtain relevant and significant data. Due to the progress of this research, classical diseases turn into syndromes of different genetic origin and so the number of diseases is growing fast. This urgently requires a reclassification of diseases based on molecular/genetic/proteomic and other markers. Heterogeneous diseases defined by purely indistinct diagnostic criteria have to be stratified into more homogeneous segments based on molecular criteria.

A potential Topic of key interest is represented by 'Studies on disease heterogeneity leading to a new taxonomy of human disease'. Selected diseases, preferably chosen from the list of priority diseases (cf. Research Priorities) and where there is a priori

evidence for heterogeneity, should be studied in sub-projects. The research should lead to identifying patterns of genes, as well as downstream biological phenomena and molecular changes closer to disease, for example, epigenetic changes, alternative splicing and post-translational modification of proteins that both predispose and protect against the selected diseases.

The impact of this initiative on the pharmaceutical industry will, in the short term, be an improvement in the diagnosis and drug development process, and, in the mid to long term a change in the drug development process with significantly reduced development timelines and vastly improved success rates and improvement in the process of developing diagnostics. Further outputs will be the identification of new targets for drug treatment, better academic/clinical understanding of the genetics of human disease and a significant contribution to a reclassification of the taxonomy of human disease. Close co-operation with other European projects addressing this issue is envisaged as well as consultation with the World Health Organization (WHO).

The application of the emerging science of pharmacogenetics to drug development may provide both the challenge and opportunity to deliver the right treatment, to the right patient at the right dose at the right time. Most drugs show a variable response and are known to carry risks of adverse effects. The biological basis for differences in individual susceptibility to diseases and responses to particular drugs has long been associated with biochemical variations of the same enzyme between individuals. This phenomenon is known as polymorphic variation, and research over the past 60 years has directly linked the sequence and biochemical behavior of variant enzymes to the sequence of the genes encoding them. Tagging SNPs are genotyped only for a selection of diseases but this is now speeding up with the application of powerful genome-wide association studies (GWAS). Currently, with the advent of affordable whole genome sequencing, genetic research is accelerating even further.

Up until now, progress in determining genetic biomarkers for drug response has generally been slow, due to the challenge of studying rare variations. Candidate and genome-wide studies that have interrogated common polymorphisms suffer from one major limitation, namely poor coverage of rare variation. To detect associations with rare variants the use of GWAS studies will be low-powered due to weak correlations between common tagSNPs and rare causal variants. The advent of ‘next-generation’ sequencing techniques makes it possible to interrogate every variable base in many samples which may solve the problem of ‘extreme phenotypes’.

The Topic of 'Genetic mapping of extreme phenotypes' is of high relevance for the progress of the understanding in the variation of drug response and risk of adverse drug effects.

The extreme phenotype approach is based on the concept that individuals at the extreme of the distribution of a particular trait have a high probability of having a mono- or oligogenic predisposition to this trait, and that these genetic abnormalities can now be elucidated at the molecular level using breakthrough technologies like exome sequencing and direct comparison of the extremes. This information can then be applied to understand less extremes variation in the phenotype, for diagnostic purposes and to develop innovative therapeutics for the condition under evaluation. In the context of drug response (both in terms of efficacy and safety), these are the individuals who are at the extremes of drug efficacy. Those who are poor responders who do not appear to benefit from treatment, those who are good responders and show the expected benefit and/or individuals that do experience severe side effects compared with individuals that do not experience any side effects at all.

The hypothesis should be tested that rare variants modify response. Depending on whether they potentiate the action of the drug, we expect to see an enrichment of such variants in the good responders and a depletion of such variants if they interfere with or block drug action. Epigenomics, trascriptomics and proteomics aspects could be advantageously embedded in the research approach. The IMI initiative should aspire to collaborate with existing initiatives such as the High Impact Project on Epigenetics. Synergy should be sought with other International funding programmes and their investigations, for example 1000 Genomes Project, E-Rare and other relevant European projects like GEFOS on genetic factors for osteoporosis, TB-EURO-GEN on genetic analysis of the host-pathogen interaction in tuberculosis, MEDALL on mechanisms of the Development of Allergy, thus avoiding overlaps.

The benefits will be the discovery of predictors of disease, which shall lead to innovative diagnostic tests, and pave the way to novel therapeutics targeted to high-risk individuals, and providing the infrastructure to select individuals for such targeted pharmacological interventions.

4.2 Rare Diseases and Stratified Therapies

(Area of Interests: Patient, Diseases, Knowledge)

While individually each disease is rare, approximately 1 in 17 people (6-8% of the population) are affected with 50% of diseases having a motor, sensory or intellectual deficiency. Two-thirds of rare diseases are genetic and therefore the recent breakthrough in genome sequencing now enables elucidation of the molecular basis of diseases, opening the door to new therapeutic approaches. While the EU Orphan Medicinal Products Regulation aims to provide effective therapies to patients with rare disease and incentives to industry to develop these therapies, there remains a need for an integrated approach to understanding the underlying disease mechanisms involved in rare diseases in order to significantly advance the number of therapeutic options available to patients. There is also a need for improving diagnostic and screening approaches to ensure that where therapy is available, it can be administered as early as possible maximising positive prognosis. Furthermore, increased awareness of rare diseases within the general public, health care professionals and clinicians is also required.

An IMI Topic on 'Co-ordinating R&D and enrolling studies on rare and neglected diseases' would be of value in reviewing potential bottlenecks in R&D on rare and neglected diseases that could be addressed through IMI. The European Medical Information System could facilitate enrolling in trials for rare diseases and obtaining samples to further disease understanding. It will be necessary to ensure that such work does not duplicate activities already being coordinated through other European R&D programmes. Projects and results of the FP7 Health theme, especially Activity 2.4.4 'Rare diseases' should be considered and engaged.

'Gender', 'age' and 'paediatrics' all define a rather rough stratification of patients. In spite of all progress in biomedical research, there is still a huge therapeutic need in these and other specific sub-groups of the population. A common feature of gender-related diseases is that the public awareness of highly prevalent diseases is very low, for example endometriosis, climaterium associated diseases, urinary incontinence, vaginal infections. Common characteristics of age-related diseases are frequently not recognised to their full extent either, for example, effects of life style - metabolic syndrome, musculoskeletal diseases (osteoporosis, spondyloarthropathies) which affect 40% of the population with increasing incidence, neurodegeneration, rheumatoid arthritis, as well as multimorbidity of old patients. In respect of paediatrics, the application of the European Paediatric Regulation contributes to the rapidly expanding number of multinational

paediatric studies and securing the specific design of preclinical and clinical studies to address children of different age is a regulatory task, but existing database resources for clinical and pharmacological epidemiologic research are rare in the paediatric population. Regarding paediatric research, the efficacy and safety assessments of drugs are restricted in children due to the small sample size of the paediatric population in clinical trials and to a short-term longitudinal follow-up. Moreover, comprehensive data on the critical group of neonates and pre-terms are scarce.

An IMI Topic on 'Paediatric medicines research' fostering the provision of multi-national, multi-source, pharmaco-epidemiological data covering all subsets of the paediatric population, would have a positive impact on the quality and the feasibility of clinical studies in children driven by the pharmaceutical industry. An active involvement of the corresponding authorities (EMA) will be requested. Investigations in other European initiatives should be considered (e.G. ECRIN), avoiding overlaps with ongoing projects in FP7 addressing paediatric research, and taking into account results from other European projects, or example TEDDY.

4.3 Systems Approaches in Drug Research

(Area of Interests: Strategies, Diseases)

Systems biology is presently a leading paradigm of life science research. IMI has the opportunity to play an active role in integrating systems biology paradigm into drug research. In light of the significant ongoing developments within systems biology the revision of the SRA will provide opportunities for future IMI calls in this field. Nomenclature and development of commonly accepted data formats are key topics for future consideration within IMI. Identifying the most relevant sectors for drug discovery and development, where systems approaches should be introduced, would also be of value. IMI initiatives in this area have high potential to develop synergy with current and planned National and European initiatives aimed to stimulate systems biology approaches for medical and clinical applications and therefore to establish the basis for systems medicine. A worthwhile topic in this area is that of 'Metabolic pathway-based drug discovery'.

Defining 'systems pharmacology' in the broad spectrum of systems biology approaches and developing new target finding strategies will lead to better understanding of mechanisms underlying disease. New drug discovery strategies, e.g. systems based drug combinations, may be expected to result directly from this approach. Such research has the potential to complement ongoing activities in the field of pharmacogenomics and

toxicity testing, which already now address a paradigm change in the field of toxicity testing towards a 'toxicity pathway' approach.

Systems approaches in drug research are by no means limited to the molecular or cellular level. An IMI Topic on 'Integrative organ-systems pharmacology' addressing tissue systems, organ systems and whole body systems and their integration into a comprehensive view on disease and potential therapies from 'molecule to patient' is recommended. Organ-systems modelling is of critical importance due to the fact that many 'classical definitions' of disease are based at the organ level. Synergies with existing European initiatives in the area (projects of Area 2.1.2 in the Health Theme, and FP7 topic 'Preparing for the future research and innovation activities in systems biology') should be considered.

4.4 'Beyond High Throughput Screening'- Pharmacological Interactions at the Molecular Level

(Area of Interests: Strategies, Tools)

Following the completion of the Human Genome Project, High Throughput Screening (HTS) has matured and become an integral part of pharmaceutical research and a cornerstone in the expansion of biomedical knowledge. The perceived failure of HTS to deliver high-quality hits is often blamed on the composition of compound libraries. Due to its better sampling efficiency, the larger space provided for medicinal chemistry operation, and the better physicochemical profile of the resulted compounds the concept of fragment based drug discovery becomes more and more popular. New optimization strategies for fragments are needed. Furthermore, new concepts for the use of genomics, proteomic and epigenomic databases have to be facilitated.

An IMI Topic addressing 'New tools for hit and lead generation' could foster the set up of a joint European compound library and potentially a screening centre. Basic compound profiling should be run in a blinded way including minimal ADME and toxicology (*in silico, in vitro, in vivo*). Co-operation with existing IMI initiatives, for example E-TOX and other European initiatives (ESFRI EU-OPENSCREEN, FP7 projects of Area 1.1 'High-throughput research' and Area 2.1 'Integrating Biological Data and Processes: Large Scale data gathering, Systems Biology' of the HEALTH theme) should be sought.

Protein structures provide important information to design new, potent and selective compounds with a better ADME/PK and toxicological profile. Massive progress in protein expression, NMR, crystallization and X-ray techniques of membrane proteins, as well as

computational approaches has been made, creating the potential for understanding pharmacological interactions at the molecular level. The understanding of kinetics (and thermodynamics) of binding is of increasing importance in drug discovery. Binding thermodynamics impact the affinity of ligands toward both targets and anti-targets. Recent reports suggest that compounds with low off-rates (maraviroc, tiotropium, montelukast) are more likely to succeed in development. However, such properties are normally found by good luck. Given the potential value of this parameter, it is somewhat surprising that there are few reports of systematic screening and analysis of compound SAR and translation to *in vivo* effects.

An IMI topic 'Towards a greater understanding of optimisation of kinetics of binding in drug discovery' would address this knowledge gap. Methods should be developed to allow information to be generated within project time scales so it could have a greater impact on compound design leading to more successful selection of drug candidates. Methodologies for the large-scale investigation and prediction of binding thermodynamics are also needed. New techniques designing compounds with specific thermodynamic and kinetic characteristic should be developed.

Nowadays the design of tailor-made ligands at a binding site to arrive at drug candidates exhibiting exactly the desired properties has become possible. In parallel to this progress, basic research in biophysics has reached a level that allows for macromolecules predictions that open the way to study pharmacology at the molecular level and to design new classes of drugs, and drugs with even more 'sophisticated' mechanisms of action in detail.

'Chemical biology' has been established as a field of research aiming at the better understanding of 'mechanisms of life' on the molecular level. While research based on (small molecule) ligand–target interaction is a common approach in drug discovery, the situation is much less straightforward in the case of an interaction by which two proteins interact with each other. Dynamics and control of such interactions are frequently determined by protein modifications, for example phosphorylation or ubiquitination. Progress in science opens now the way to integrate new knowledge and new methodologies into the drug discovery research. For example, the field of protein ubiquitination is rapidly becoming an area of considerable interest for both academic and industrial drug discovery activities. However, despite rapid accumulation of data identifying novel therapeutic targets within the ubiquitin family, the ability to ‘drug’ these new targets remains relatively poor due to a lack of understanding of the wider target class and available tools such as recombinant proteins, structural information, assay

platforms, inhibitor chemotypes and target associated biology. An IMI Topic addressing the challenges of understanding 'protein/protein interaction', and protein modifications such as 'ubiquitin ligation', to generate new methods and tools for this emerging area of drug R&D would be of value. Results from ongoing European projects, like Predict-IV 'Profiling the toxicity of new drugs: a non animal-based approach integrating toxicodynamics and biokinetics' should be considered.

4.5 API Technology (Drug Compound Development)

(Area of Interest: Development)

Industrial manufacturing of Active Pharmaceutical Ingredients (APIs) based on the development of appropriate technologies has also been an inherent part of the preclinical drug development process, subject to good manufacturing practice (GMP) and strictly supervised by regulatory authorities for more than a decade. Nevertheless, the enormous relevance of the transformation of (laboratory) syntheses into manufacturing technologies, which meet, among others, regulatory, legal and economic requirements, is not yet fully recognised.

Improving the sustainability of manufacturing processes is critical to ensure the economic competitiveness of Europe´s chemical and pharmaceutical manufacturing base, while improving environmental quality in the region. The pharmaceutical industry is devoted to inventing medicines that allow patients to live longer, healthier and more productive lives. In addition these pharmaceutical companies are also committed to bringing key medicines to the patient with minimum impact on the environment. The launch of an IMI topic on 'Sustainable Chemistry' provides an ideal framework upon which to develop a synthetic capability to meet the needs of sustainability in the 21st century through a 'benign by design' approach. In order to ensure the sustainable delivery of drugs to patients in Europe (especially as the population ages) and ensure European R&D and manufacturing competitiveness, it is critical to develop innovations in chemical synthesis and manufacture. For example, while material consumption, waste treatment, and costs are obvious 'sustainability' concerns for the pharmaceutical industry, another less apparent concern is the emerging scarcity of precious metals currently used to synthesize most medicines. Ubiquitous catalysts such as platinum are being depleted at alarming rates, with some estimates indicating depletion past economic viability within 30 years. Such precious metal catalysts have been key to improving mass efficiency over the past 50 years, and their disappearance could result in substantial efficiency losses unless substitutes are found.

The discovery of green and sustainable synthesis methodologies is a long-term (> 3 years) endeavour and currently the expertise predominantly lies with academic researchers. Historically, pharmaceutical R&D has routinely implemented methodologies developed in the public sector rather than driven the 'in-house' discovery of fundamentally new transformations. To increase the efficiency and impact of this research on European medicines development it is essential to combine the skills and expertise that reside in the public sector with the knowledge of the most problematic reactions that reside within industry.

Batch production technologies prevail in pharmaceutical industry. Although continuous processes are fully established in other branches of chemical industry, the situation is still absolutely different concerning the development of technologies for API manufacturing. Due to the manifold superiority of continuous processes, for example their combination with the application of microwaves, an initiative on 'Flow chemistry' should be set up to promote research activities towards establishment of flow chemistry.

4.6 Advanced Formulations

(Areas of Interest: Development, Diseases)

The design of the product including selection of active drug solid state forms can strongly influence the clinical safety and efficacy primarily through controlling drug exposure in the body. This can be used to optimise the clinical utility of drug products. For example, in the area of Modified Release (MR) formulations, new developments in areas of biomarkers and translational science hold promise to identify optimal drug exposure time profiles in the body better than can be realised through existing MR technologies. Another example is formulation approaches that increase the extent of exposure. The modern drug discovery approaches results in larger, more hydrophobic drug molecules increasing the need for such bioavailability enhancing formulations. They may not only ascertain that therapeutic drug levels are reached but also reduce drug exposure variability in patients.

Although scientific progress in pharmaceutical technological development has been impressive, there is still a demand for more efficient translation of this progress into industrial practice. Pre-competitive approaches will be identified to promote advanced formulations and to remove bottlenecks in the development of drug delivery systems, formulations, in particular for oligonucleotide, peptide and protein-based medicines.

The influence of the pharmaceutical properties on drug exposure also has great implications ascertaining the safety and efficacy of marketed drug products. Novel approaches according to the 'Quality by Design' concept have put an increased emphasis on the clinical relevance of pharmaceutical quality criteria.

Design and development of new pharmaceutical materials including excipients, exploitation of sensor technology and microelectronics in drug formulation and delivery, more efficient manufacturing processes including miniaturised and continuous processes and optimising biopharmaceutical characteristics of final drug products are major issues in this field.

The oral route is by far the preferred route of administration of medicines. But the introduction of new highly active compounds with poor bioavailability, the growing awareness of food effects, the growing appreciation of the influence of the extremes of age on bioavailability warrant precompetitive research to study oral formulation development. An IMI Topic on *'In vivo* predictive biopharmaceutics tools for oral drug delivery' is recommended in order to foster the development of new methods and validation of existing biopharmaceutics modelling/prediction tools for medicine performance in practice. 'Delivery and targeting mechanisms for biological macromolecules' is a topic of high interest in this Research Priority.

Therapeutic modalities based on macromolecules of biological origin, e.g., proteins, peptides and oligonucleotides, have a huge pharmacological potential due to their highly selective mode of action, and some of them have activity against targets that are considered 'non-druggable' by more traditional small organic molecules. Similarly, therapeutic oligonucleotide medicines for the most part interfere with gene translation and transcription and are currently being evaluated for treatment of diseases with currently 'non-druggable' molecular targets. Although the target selectivity is usually very high for both peptide and oligonucleotide-based drugs, dose-related adverse events are not uncommon. There is still room for major improvements in therapeutic margins to minimize the potential for off-target effects via strategies focused on improved (targeted) delivery and dose reduction. Potential disease targets are cancer, diabetes, Alzheimer's disease, muscular dystrophy, cystic fibrosis, and as well as a range of rare or orphan diseases that may not be addressable using traditional NCE based pharmacology.

4.7 Stem Cells for Drug Development and Toxicity Screening
(Area of Interest: Tools)

Stem Cells are at the cornerstone of a paradigm shift in drug development. Human-induced pluripotent stem cells (iPS-cells) and their derivatives present an emerging system with the potential to replicate drug responses in man, addressing disease mechanisms and able to predict both efficacy and safety.

Drug Safety (preclinical and clinical toxicity) accounts for the failure of approximately 40% of all molecules in the development pipelines of European pharmaceutical companies, while lack of efficacy is the second leading cause of attrition for molecules in the development pipelines. Scientific advances and interest in stem cell research have developed very rapidly in the past few years with increasing impact on drug discovery. In 2006, Shinya Yamanaka first reprogrammed somatic cells (fibroblasts) to an embryonic stage naming them 'induced pluripotent stem cells (iPS)'. Since this breakthrough, many academic and industrial laboratories around the globe have reproduced these findings and made significant improvements to the original protocols.

It is now straightforward to use skin biopsies from patients to produce patient specific iPS cells. With such iPS cell-lines one could theoretically derive all ~200 different cell types of the human body, providing the unique opportunity to develop patient specific stem cell-based in vitro assays as tools for drug discovery and safety testing. The proposed area could support national efforts in the field of toxicity testing that aim for implementation of new technologies as alternatives for drug testing in animals.

Stem cells may be used as tools, targets and therapies. In spite of the progress there is still a lot to do to integrate stem cells into drug research. Main objective within IMI will be the development of novel pharmacological tools based on adult stem cells, identification of the most suitable stem cell type for building 3-D tissue models, assessing the safety aspects of stem cells and above all their applicability on toxicity testing.

Further relevant outputs could be the standardisation of nomenclature, suggestions for common ethical, legal and social frames for use of stem cells, fostering of bio-banking, and in general an accelerated improvement of the technology and its standardisation. Cooperation with existing (ESFRI BBMRI) and upcoming initiatives, dealing with innovative strategies for translation of stem cell based therapies in regenerative medicines will have to be sought.

4.8 Integration of Imaging Techniques into Drug Research
(Areas of Interests: Tools, Disease)

Imaging approaches have a high potential to support the development/evaluation of new therapeutic interventions. More and more often they are also being introduced to support the individualised medicine paradigm, for example, imaging-guided therapies, imaging diagnostic biomarkers, magnetic particle imaging, nanomedicine and theragnostics.

While in human diagnostics imaging methods are well-integrated and steadily growing in importance, there is still a huge unexploited potential for application of imaging methods in pre-clinical drug development, above all in pharmacodynamic studies used primarily for identifying efficacious exposure ranges to move forward into clinical development. Significant efforts towards standardisation and validation of existing functional imaging techniques are required to speed up integration of imaging methods into regulatory controlled drug development. The success rate of drug development in clinical trials for Central Nervous System (CNS) disorders has been hampered by the difficulties to assess efficacy, to identify surrogate markers and to assess tolerability. Moreover, the lack of clear understanding of biological mechanisms underlying various CNS neurological disorders such as Multiple Sclerosis, Parkinson, Alzheimer's disease, pain etc., the low translatability of preclinical models and the sensitivity in methods of measurements specific to distinct pathological traits have prevented further progression. These gaps result in the need for large, long, expensive clinical trials to reach clinically significant endpoints, because of a lack of early decision-making abilities. There is an increasing interest to use functional MRI (fMRI) as a clinical tool to study effects of drug treatments and disease progression/modification in CNS indications and pain.

It is a relevant IMI topic to address the clear needs for the development of robust and practical functional imaging schemes that are appropriately translatable from preclinical models to the clinical area, validated and standardized across laboratories and hospitals and the public and private sector. Furthermore the use of a multimodal approach would allow validation of MRI-results based on BOLD or CBV imaging, with high test-retest variability, with alternative methods such as PET using FDG-PET or H2O15-PET, with excellent test-retest variability, an important point in longitudinal studies, including challenge studies. Close cooperation between IMI projects and other European imaging projects and, for example, Joint Programming Initiative on Neurodegeneration, ESFRI European Biomedical Imaging Infrastructure from molecule to patient (EuroBioImaging) should be aspired to and overlaps should be avoided.

5 The 10 Established Key Research Priorities.

In the first SRA (2008) four research pillars were identified: Efficacy, Safety, Knowledge Management and Education/Training. In addition there were a number of targeted disease areas. Call topics have been derived from this first SRA (see Table 1 and 2 earlier in the text).

In order to further promote IMI's focus on 'game-changing' ideas and areas where the maximum number of companies can join forces, we are updating this framework which identifies 10 key Research Priorities ('pillars' plus 'disease themes') that IMI has selected and will use for its strategic planning in future, in conjunction with the new Research Priorities already presented in the previous section.

5.1 Safety Sciences

(Area of Interest: Development)

This continues to be a high priority for future IMI calls. Areas of Interest will be methodological studies for validation studies, safety, modelling and simulation, in tight coordination with other European initiatives in the area of 'in-silico' drug testing. In this context a topic on 'Assessment of drug-induced toxicity in relevant organs – Surrogates for early drug failure' would be of high relevance for IMI in close collaboration and synergy with other European research initiatives on biomarkers, drug safety and human safety assessment (e.g. FP7 Call on Alternative Testing Strategies).

Another important topic is 'Cardiovascular safety'. A number of sources of information strongly implicate cardiovascular safety as a major concern in drug discovery & development and post-marketing. Adverse events can be structural or functional: in the heart, for example, they can range from effects on electrophysiology, contractile activity and structure. Also, they can be acute or may only be apparent following chronic dosing. An integrated strategy, moving from *in silico* to *in vitro* and *in vivo* testing pre-clinically, and culminating in measurement of translatable end-points in man, should be the aspiration for those addressing cardiovascular safety. Though it needs to be acknowledged that such is the biological complexity involved, that complete, integrated strategies will not be possible in all areas, it is important determining what assays/screens/models/biomarkers could realistically form a predictive strategy for cardiovascular safety concerns.

5.2 Increasing Practicability of Biomarkers and Biobanks

(Areas of Interest: Tools, Knowledge)

One major challenge for IMI going forward is to ensure that there is effective coordination on the establishment and management of biobanks with ongoing European infrastructure initiatives such as BBMRI and other ESFRI BMS programmes. It has been agreed that cross-IMI project standards for biobanks should be considered within a new KM governance mechanism.

5.3 Coping with Regulatory and Legal Hurdles

(Area of Interest: Development)

The validation and qualification of biomarkers for use in clinical development and increased demand for observational data, for example patient reported outcome data, will ultimately lead to the development and implementation of innovative clinical study designs including patient stratification and replacement of clinical endpoints with biomarker readouts.

IMI initiatives dealing with 'Regulatory aspects of personalised medicine and novel therapies' will provide the opportunity to understand the scientific aspect of regulatory issues of novel technologies better. This is in general within the EMA's '2020 Roadmap', and the EMA's current involvement/interest in IMI would allow further activity in this area, if needed (particularly relevant for stem cells) with ESFRI BMS programmes and especially ECRIN will have to be considered.

Another potential Call Topic relevant to this area is that aiming to the 'Introduction of observational data earlier in clinical development'. The demand for data demonstrating the value of new medicines has increased dramatically, placing increasing burden on the evidence generation process throughout medicine development. Traditionally, decision-making in the clinical development process has been driven by clinical outcome data defined to meet regulatory requirements. However, in many cases such data do not capture the full benefit of the drug as perceived by patients. There is a growing need to improve the generation and use of observational data through drug development to more fully define the unmet need, the capacity for benefit from new medicines and indeed the full range of benefits provided by new therapies which in turn helps payers make improved decisions about access for their populations. An integrated approach combining clinicians, methods experts, academic and industry scientists, economists

regulators and payers will be required to integrate the use of observational data throughout drug development.

The greatest unmet medical need lies in the most complex diseases, many of which are chronic in nature and are becoming more prevalent with a growing aging population. A significant contribution to win this challenge would be an IMI topic on 'Combination Therapy Development'. Combination therapies have the potential to be more effective than single therapies by targeting multiple disease pathways. However, presently the inefficiency underlying the development of such approaches is hindering progress in this area. Furthermore, the increasing polypharmacy of patients would greatly benefit from simplification strategies. Fixed-dose combination products (FDCs) represent a clear means of improving patient compliance and clinical outcomes especially in 'vulnerable' patient groups like elderly or paediatric patients with severe chronic illness and/or mental disease.

The main obstacles to the development of combination therapies relate to product quality, safety and efficacy issues. The process has to ensure that the co-administration or mixing of separate active ingredients does not raise new drug–drug interaction issues or compromise product pharmacokinetics and ultimately efficacy. Requirements to demonstrate efficacy and safety of a combination therapy have historically relied on the principle of fully demonstrating the properties of the individual components and also of the combination. Other than the guidelines on fixed combinations (CHMP/EWP/240/95 Rev.1 and CHMP/EWP/240/95 Rev.1), there are no uniform principles, guidelines or international standards addressing the development and regulatory assessment of combination therapies. This has led to poor acceptance from the scientific community, poor availability of combination therapies, limited epidemiology data, and lack of appropriate model systems as few or no up-to-date study methodologies and regulatory strategies. An IMI Topic on 'Combination Therapy Development' could significantly contribute to change this slow, inefficient and expensive approach addressing technological challenges in relation with for example combining new active substances with devices and fixed combination products.

Overcoming hurdles in combining existing therapeutic agents will not only deliver more effective treatment paradigms but will also have the potential to drive change in the fundamental approach to drug discovery which currently focuses on one drug for one mechanism and disease. A more efficient approach to the development of combination therapies from the outset of drug development, could lead to the ability to target more than one mechanism at a time.

5.4 Knowledge Management

(Areas of Interest: Knowledge, Patient, Development)

'New knowledge' is the main product of IMI activities. At the same time existing knowledge is a fundamental requirement in IMI research. Therefore, Knowledge Management has a specific position within IMI.

The following operational definition of knowledge management will be used for implementation purposes. Knowledge management is defined as the e-collaboration platforms enabling efficient collaborations in and between PPP partnerships such as the IMI partnerships, document and content management, data management including analysis, modelling and data pooling tools as well as bio-banking. In short, this comprises digital asset management.

To make scientific data useful for other scientific fields, data should be widely accessible by design. Almost all disciplines[2] are confronted with the 'digital data deluge', and therefore need to find ways to manage their records and to solve the retrieval problem.

This can be achieved through the following;
- descriptive metadata, describing the resources and services in order to find proper resources and services (usage, standardisation, interoperability, quality, earliness, scope, provenance, persistence, aggregations, and availability of descriptive metadata.
- the quality of data resources (description, sharing, quality assurance, assessment of the quality of data resources), in order to allow peer review of the quality of the research but more importantly allow reuse of data in testing new hypotheses including specific pooling of data to answer specific research questions, and
- interoperability (resource-level, general, syntactic versus semantic interoperability). In order to achieve technical interoperability, standards will have to be applied.

Interoperability is mostly isolated within individual communities, driven directly by community-specific projects, standards, or to meet urgent needs. Interoperability between individual communities and biomedical fields, between research and development is a particular bottleneck especially in translational research. Whereas there is a basic schism in data models and semantics between the fields of patient care

[2] - e-IRG Report on Data Management: The e-IRG report on Data Management was jointly endorsed by the e-IRG, on 30 November 2009, and by ESFRI, on 11 December 2009
- OECD 13 principles and guidelines for access to research data from public funding
- Semantic HEALTH Report 2009 Semantic Interoperability for Better Health and Safer Healthcare

and clinical research (one of the difficulties in the reuse of electronic healthcare data for clinical research), progress has been made towards interoperability in the clinical research field.

For Healthcare, as a high-ranking structure, a Reference Information Model (RIM) was established. In this context, HL7 v3 offers specifications for data types for health care, XML data formats for medical information, and controlled vocabulary and specifications for the Clinical Document Architecture (CDA). In the domain of clinical research, standards provided by CDISC are used. The mission of CDISC is to develop and support global, platform-independent data standards that enable information system interoperability in order to improve medical research and related areas of health care. CDISC-based standards cover the following models:

- Operational Data Model (ODM),
- Study Data Tabulation Model (SDTM),
- Analysis Dataset Model (ADaM),
- Laboratory Data Model (LAB),
- Protocol Representation Group (PRG),
- Standards for Exchange of Non-clinical Data (SEND),
- Case Report Tabulation Data Definition Specification (CRT-DDS), and
- CDASH, specifying the data collection fields for 18 domains for case record forms.

Both worlds are bridged by a specific domain model. In general, domain modelling conceptualises a domain, and this conceptualisation is represented in computable knowledge as ontologies or domain analysis models. In this way the Biomedical Research Integrated Domain Model (BRIDG) focuses on the abstract meaning of concepts shared by clinical research communities. BRIDG, a shared domain analysis model of regulated clinical research, builds a connection with the Reference Information Model (RIM) of Health Level 7 (HL7). Recently, the CDISC Protocol Representation Model (PRM), which identifies and defines a set of over 300 study protocol elements, was used to map PRM elements to elements of the BRIDG model. This is especially important, because the protocol is the core part of every clinical research study. Thus, PRM protocol information can be readily extracted and entered automatically into information systems or online registries, supporting the general goal of more transparency in clinical trials.'

Additionally, standards need to be expanded beyond the clinical research area and there is a need for open standards. 'Open standards', meaning, that anyone is free to implement them unencumbered by licences or patents at any point from today into the

future, are often essential to achieving interoperability in this wider context, beyond a single community. It is often important to have a Standards body, not just a single company or institution 'owning' the standard. It is also often helpful if the Standards group is open to participation as large membership fees can prevent smaller communities or academic institutions from participating in the standards process.

In order to address these challenges, collaboration with existing data initiatives is needed to ensure appropriate handling of the data within IMI and to provide models and governance for the reuse of the data generated in the research projects as well as to test new hypotheses and to provide models for the pharmaceutical companies to solve the data sharing and interoperability issues between different scientific domains within pharmaceutical R&D. Translational research (TR) in drug discovery and development requires sharing of knowledge between pre-clinical and clinical activities in order to derive new insights into disease presence, progression, drug response and drug toxicity. This translational philosophy is at the heart of the IMI pre-competitive mission between the EC and the European Pharmaceutical Industry.

As expected, such TR involves significant knowledge management challenges, as outlined in the IMI Scientific Research Agenda (v2)(2008), Section 4.0. In particular, these challenges include access, management, integration and analytics across diverse datatypes, such as clinical, eHR, biobank, *in vivo, in vitro*, omic, bioimaging and prior knowledge plus others. These information challenges are too broad to be addressed in a single IMI call but instead will require the coordinated EFPIA steer onto a wide range of PPP investments across the EU. While the scientific community develops a knowledge management (KM) strategy, it is clear there is a need for focused Knowledge Management provision for existing and future IMI Calls, for example, 1st Call project U-BioPRED, incorporating both preclinical and clinical data to ensure they maximise their potential. Currently every translational study requires bespoke data management and analysis investments resulting in unnecessary significant overheads, intellectual property complexity, and importantly, a lack of translational information and ‘know-how’ sharing. The proposal is to establish a European physical infrastructure and service is to establish via an IMI 'Translational Study KM Infrastructure & Services,' to

- provide the necessary supporting capability for IMI calls and other EU translational projects, and
- aid the coordination across the various related bio-medical infrastructure and standards activities pertinent to this complex domain.

Whereas such a platform would have been useful for the very first IMI projects, it is considered that it will be useful for future IMI Calls as well as ongoing projects who have not yet adopted a solution.

Synergies with existing initiatives with regard to Knowledge Management have to be assured, for example, ELIXIR and standardisation organisations such as CDISC. All aspects of intellectual property, data protection and data confidentiality will have to be considered in advance. Such a translational knowledge management platform potentially could support a wide range of different research and R&D areas. Due consideration should be given to the best platform to be adopted or developed, as well as to how best to maintain and enhance such a platform using 'open source' software development methods or others.

Another potential topic for this area is that leading to a European Medical Information Framework for patient-level data in support of a wide range of research studies' such as extreme phenotypes and disease management and outcomes. Healthcare Organisations and the pharmaceutical industry in Europe both share a common goal, which is to improve patient outcomes by delivering the best possible personalised treatments and innovative medicines. The development and implementation of a European Medical Information Framework (EMIF) that provides access to comprehensive and in-depth data on a large scale for addressing the above research topics requires a massive effort that spans a number of contributors and experts from the pharmaceutical industry, healthcare organisations, academia and other third parties throughout Europe. Such effort would be proficiently addressed by an IMI Topic on 'a European Medical Information Framework for patient-level data in support of a wide range of research studies' Electronic Health Records (EHR) contain an enormous wealth of medical information that has the potential to significantly improve healthcare and advance medical research. The industry believes that technological advances and broad implementation of EHRs in Europe are necessary to realise this potential.

Direct applications of a linked-up network of such data sources across Europe are numerous. Of particular relevance are the elucidation at the molecular level of diseases and drug response using an extreme phenotype approach, insight into geographical disparities in disease management and outcome and evaluation of treatment benefit/risk ratio. This effort should start with 1 or 2 focused research projects using readily accessible data sources whilst ensuring that the framework can be expanded for future research projects. It is important to duly consider all aspects of intellectual property, data protection, data confidentiality and data access within and beyond IMI projects. To

this end cooperation with, and complementarity to other relevant European initiatives in the area of health records and their re-use is essential. This area includes topics such as tools and environments enabling the re-use of electronic health records for clinical research, patients´guidance services for personalised management of health status, decision support systems, development of ICT tools, services and infrastructure to obtain large repositories of re-usable data and models, data quality, data protection, interoperability and standards.

5.5 Science Communication

(Areas of Interest: Knowledge, Diseases, Tools)

Communication, training and education, including and integrating aspects like 'communication to the public' are key to strengthening the European Scientific Community in drug research and represent important IMI activities.

Primarily, it is very important to consider the sustainability of programmes of the 1st Calls Topics, ensuring that the identified relevant emerging needs are considered and rapidly implemented in corresponding training programmes, when setting up the future priorities in science and communication. It is of utmost importance to link these programmes to a future Call for proposals in science and communication. Future Calls could cover gaps identified in the SRA which still constitute a priority and need to be addressed, which include dedicated programme in translational medicine science, biostatisticians programme, bioinformaticians and biomedical informaticians programme, Regulatory affairs-based programmes, regulatory dossier, format for a registration dossier (non-clinical, clinical and quality), intellectual property (IPR), new technologies, advanced therapies, rare diseases. Also the concept of personalized medicine and the potential of genetic information require attention. The target audience should include practicing clinicians as well as the general public.

5.6 Neuro-psychiatric Disorders/Brain Diseases

(Area of Interest: Disease)

This disease area has been focus of Topics in the 1st and 3rd IMI Calls. Nevertheless proposals relevant to brain diseases should be maintained in the SRA as it is revised. Mental illness is responsible for around 25% of disability and death in the developed countries (a higher figure than for cancer), but discovery of new drugs for CNS disorders is very difficult and very expensive. There are major problems in translating from

preclinical models such as mice to patients and diseases. Most drugs that have so far reached the market have been discovered via a serendipitous approach.

Potential challenges that may be relevant include the application of epigenetics, a greater understanding of the 'blood-brain' barrier and further development into the identification and validation of pre-symptomatic and surrogate markers for disease progression, as well as other topics leading to enhancing of translation in neurological disease.

Neuropsychiatric disorders are highly complex in origin, with multiple genetic factors combining with individual development and environmental experience to generate patterns of behaviour that we classify as single disease entities. In the absence of a clear understanding of the molecular bases of these disorders, rational drug discovery has concentrated on improving the tolerability, PK and toxicology of compounds whose basic mechanism of action were initially discovered serendipitously. This problem has led to the search for animal models of diseases which are really syndromes, with validity being apparently underwritten by simulating the effects of those compounds that exert some therapeutic benefit in man. The result of this approach is that we only discover what we already know and many symptoms of the diseases remain poorly or not at all treated by the current medications.

Despite the diagnostic labelling, common factors, symptom clusters or endophenotypes can be seen to be dysfunctional across broad diagnostic categories. This challenge can be addressed by an IMI topic on 'Treating mental illness symptom clusters across disease classifications'. In such an initiative, starting from our knowledge of the biology of affect, motivation, arousal and cognition, an alternative approach to drug discovery might be developed to examine the neurobiology and pharmacology of the endophenotypes within these broad functional domains via a translational neuroscience and experimental medicine approach. The initiative should build and consider results from other European initiatives such as the epidemiological findings of the CSA which is due to start activities in 2011, addressing the topic 'HEALTH.2011.3.3-4: A road-map for mental health research in Europe'.

Another key area of unmet need for the R&D of CNS disorders is 'The understanding of the pathophysiology of chronic neurodegeneration', which is necessary for the successful development of disease-modifying treatments and the development of models and tools adequate for the R&D demands. An IMI topic in this area should carefully evaluate its niche taking in consideration and creating synergies with other ongoing IMI (PharmaCog)

and European initiatives in neurodegeneration (most notably the Joint Programming Initiative on Neurodegeneration).

The topic 'Examining the role of the Blood-Brain Barrier in the immune protection of the brain' is also relevant to solving bottlenecks in CNS R&D area. IMI initiatives in this subject will have to be carefully designed to create synergies and not to overlap with other European initiatives that already exist or are being planned.

Available drugs for Parkinson's Disease (PD) may control the symptoms, but none of them treats the disease. The creation of animal models in which to evaluate potential biomarkers has been hampered by the lack of specific PD models in which early signs of the illness are observed (i.e., olfactory impairment) and neuronal degeneration takes place progressively. An IMI Topic on 'Peripheral and central biomarkers in animal models of Parkinson's Disease' should be considered to generate a collaborative and integrative effort between academy and industry to successfully tackle this challenge.

5.7 Inflammatory and Immune-Mediated Diseases

(Area of Interest: Disease)

Inflammatory and immune-mediated diseases affect many people and represent the greatest collective burden of suffering and economic cost in the developed world. New drug development in this field has been hampered by a lack of validated / accepted measurements that can be used as intermediates in intervention studies to target disease manifestation and identify more homogeneous subgroups of patients. In addition, certain pre-clinical models lack key structural features of the human disease. Moreover, many medications give only symptomatic relief, rather than treating the underlying medical condition, increasing the need to identify new treatment approaches and/or safer, more efficacious pharmacological therapeutics. Although inflammation and immunology were already considered in previous IMI Calls, many significant challenges remain, indicating that the revised SRA should keep this area as a priority.

A possible IMI topic of value in this area is on the 'Assessment of Acute Inflammatory Diseases'. Acute inflammatory responses are commonly discussed to be the primary cause of diseases like acute lung injury / acute respiratory distress syndrome (ALI/ARDS), acute kidney failure (AKI) or multi-organ dysfunction syndrome (MODS). Despite continuous improvements in intensive care medicine the mortality for these diseases still remains high, indicating a urgent medical need for therapy in acute inflammatory diseases.

Other topics worthy of IMI attention are those of 'Resolving the challenge of chronic inflammation and autoimmunity, including COPD, asthma, multiple sclerosis and lupus erythematosus' and on 'Inflammation as a component of cancer'. As already several projects in the field are funded at European level, close cooperation between IMI projects and other European projects has to be ensured in this area and overlaps should be avoided.

A harmonised approach involving government, academic institutions, hospitals, and pharmaceutical companies is necessary to facilitate the identification and validation/ qualification of biomarkers and/or clinical intermediates to overcome limitations in pre-existing data-sets and effectively combine knowledge and expertise in this field to gain the necessary critical mass to address unmet medical need in this area.

5.8 Cancer

(Area of Interest: Disease)

A number of key bottlenecks in oncology research are already being addressed in the first IMI Calls, but cancer research should clearly remain in the revised SRA. Cancer is a heterogeneous group of diseases and the research focusing on these pathologies is therefore complex and multidisciplinary. There are more than 100 types of cancer. Due to the significant discrepancies in survival rates patients urgently need more efficient drugs to treat this disease. This will require a better understanding of the genes involved in cancer development, most ideally those which are shared by different cancer types. So far, only 392 genes of the human genome are targeted by a total of 884 drugs with human target genes. Thus the arsenal of about 250 cancer drugs is directed to only a limited number of genes.

A great number of 'redefined' cancer subtypes create massive demand for specific clinical studies. There may be opportunities for IMI to reshape clinical studies (e.g. investigator-initiated trials). The revised SRA could enable IMI to stimulate opportunities into a wide range of technologies in oncology research, particularly in the development of new predictive in vitro/in vivo models, including methods for early characterization / diagnosis of cancer patients (pre-metastases). Focus should primarily be on cancers where no satisfying characterisation approaches are available like e.g. lung, gastric, ovarian and liver. Some aspects have already been addressed in initial IMI Calls (cancer biomarkers, tumour imaging) and may not be a priority for future calls. Stem cell research is likely to be a priority.

5.9 Metabolic Diseases including cardiovascular diseases

(Area of Interest: Disease)

A number of challenges regarding metabolic disease research were identified in the original SRA and have been taken forward through the initial calls of IMI. Nevertheless, there will be further ongoing assessment of collaborative opportunities on all aspects of metabolic disease-based research. Co-operation and opportunity for project-clustering with other European initiatives in the fields of cardiovascular diseases, diabetes and obesity, including topics for computer based models and simulation of major diseases integrating environmental data would increase the impact. The results of the DIAMAP Report should be taken into account.

5.10 Infectious Diseases

(Area of Interest: Disease)

Bottlenecks in Pharma R&D into infectious diseases were identified in the initial SRA but new proposals are likely to arise in future IMI Calls. IMI will not seek to duplicate other European research programmes. Potential future IMI programmes may be focused more into developing a greater understanding of the immune status of the host (for example, a human pathogen immune project examining translatable animal models, profiling immune cells, understanding host responses among others) and antimicrobial resistance. The continued emergence of drug resistance among commonly encountered pathogens and the evolution of multi-drug resistant pathogens refractory to the majority of currently utilised therapeutics represent challenges for the treatment of infectious disease both today and in the future. Infectious diseases remain the second leading cause of death worldwide and are the third leading cause of death among the developed world. These developments have created an increasing need for new antimicrobials that will enable clinicians to manage infections caused by these pathogens better. However, antimicrobial research and development has been less of a focus of the pharmaceutical industry than in the past. Although new leads continue to be generated from both the pharmaceutical and biotechnology industries that have remained committed to generating new antimicrobials, various challenges including regulatory approval have made it more difficult to get these compounds through the drug development pipeline and into the market. IMI offers the opportunity for an integrated approach to tackle this growing health issue. Activities of the recently established "Joint Programming Initiative on Antimicrobial Resistance" as well as the ERA-NET PathoGenoMics should be considered and complemented.

6 List of Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
ADaM	Analysis Dataset Model
AKI	Acute kidney Injury
ALI/ARDS	acute lung injury / acute respiratory distress syndrome
API	Active Pharmacological Ingredient
BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
BRIDG	Biomedical Research Integrated Domain Model
CDA	Clinical Document Architecture
CDASH	Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CRT-DDS	Case Report Tabulation Data Definition Specification
CSA	Co-ordination and Support Action
EC	European Commission
eHR	Electronic Health Record
EFPIA	European Federation of Pharmaceutical Industries and Associations
ECRIN	European Clinical Infrastructure Network
EMA	European Medicines Agency
EMIF	European Medical Information Framework
ERA-NET	European Research Area Network
ESFRI	European Strategy Forum on Research Infrastructures
ESFRI BMS	European Strategy Forum on Research Infrastructures Biological Medical Sciences
FDC	Fixed Dose Combination
FP7	Framework Programme 7
GWAS	Genome Wide Association Study
HIP	High Impact Project
HTS	High Throughput Screening
ICT	Information and communication technologies
IMI JU	Innovative Medicines Initiative Joint Undertaking
IPR	Intellectual Properties Rights
KM	Knowledge Management
LAB	Laboratory Data Model
MR	Modified Release
NCE	New Chemical Entity
NMR	Nuclear Magnetic Resonance
PD	Parkinson's Disease
ODM	Operational Data Model
PK	Pharmacokinetics

PRG	Protocol Representation Group
R&D	Research and Development
RDG	Research Director Group
RIM	Reference Information Model
SC	Scientific Committee
SEND	Standards for Exchange of Non-clinical Data
SME	Small Medium Enterprise
SRA	Scientific Research Agenda
SRG	States Representatives Group
SDTM	Study Data Tabulation Model
TR	Translational Research
UBL	Ubiquitin-like
WHO	Word Health Organization