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COMMISSION STAFF WORKING DOCUMENT

Use of '-omics' technologies in the development of personalised medicine

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1. AIM OF THE STAFF WORKING DOCUMENT

Under the heading ‘*Towards more personalised medicines*’ in its Communication¹ of 10 December 2008 on a Renewed Vision for the Pharmaceutical Sector, the Commission announced a report on the use of ‘-omics’ technologies² in pharmaceutical research and development.

This report, presented in the form of a staff working document, focuses on:

- the potential and issues with the use of -omics technologies in the research and development of personalised medicine and current EU research funding in the area;
- recent developments in EU legislation for placing medicinal products and medical devices on the market;
- factors affecting the uptake of personalised medicine in health care systems.

2. INTRODUCTION

Although no official definition of personalised medicine exists, for the purpose of this document, and given its context, *personalised medicine refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.*

This rapidly developing science-driven approach to health care has potentially very great benefits for patients, clinicians and health care systems alike. Some potential advantages offered by this new approach include:

- Ability to make more informed medical decisions;
- Higher probability of desired outcomes thanks to better-targeted therapies;
- Reduced probability of adverse reactions to medicines;
- Focus on prevention and prediction of disease rather than reaction to it;
- Earlier disease intervention than has been possible in the past;
- Improved health care cost containment.

Pharmaceutical development has led to thousands of medicines available worldwide, but many medicines are not as effective as expected in all patients, and some patients may suffer from serious adverse reactions.

The reason for this is that therapies traditionally have been developed, and prescribed, using an ‘average patient’ approach that does not take into account patients’ ‘molecular make-up’, a

¹ COM(2008) 666 final Communication from the Commission to the European Parliament, the Council, the European Economic and social Committee and the Committee of the regions - Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector

² ‘Omics’ technology is a general term for a broad discipline in science and engineering for analysing the interactions of biological information objects in various ‘omes’ that include the genome, proteome, metabolome, transcriptome etc. Its main focus is on developing technologies and tools for gathering information on various classes of biomolecules and their ligands, and understanding relationships among them, including the related regulatory mechanisms.

factor that, together with environmental and lifestyle factors, determines susceptibility to disease, the course of disease, and response to treatment.

Personalised medicine starts with the patient. However, rather than having a unique treatment for each individual person, patients are sub-divided into groups based on their ‘molecular make-up’, e.g. using biomarkers³. Through this stratification of patients, medical interventions can be tailored to be more efficacious in a particular group of patients than under the currently dominant ‘one size fits all’ approach where no stratification is done. In addition, clinical implementation of genomic biomarkers may allow predicting which patients are at high risk of serious adverse reactions, e.g. in relation to genetic variants of metabolism enzymes, transporters or genes active in the immune responses underlying idiosyncratic reactions. This may optimise the dosing and selection of medicines and thus reduce the occurrence of adverse reactions to treatment, estimated to be the cause of over 6% of hospital admissions⁴.

Following the sequencing of the human genome about a decade ago, many new ‘-omics’ disciplines have emerged. These new disciplines are key to the development of personalised medicine as they contribute to the understanding of disease at molecular level and to the identification of new biomarkers as quantifiable parameters predictive of the development of a disease, disease prognosis or medicine response or as targets for new treatments. The ultimate goal is to move towards prevention or early treatment of diseases and to ensure that medicines that are both tailored to individual patients and address public health needs are available in good time.

As research progresses and our understanding of disease at molecular level advances, the taxonomy of diseases may be redefined. Science has already begun to demonstrate that diseases historically seen as one disease are in fact a collection of diseases influenced by different pathological mechanisms demanding different treatment strategies. On the other hand, diseases that today are considered as different diseases have been shown to share the same disease mechanism at molecular level. Treatments targeting a specific molecular mechanism could therefore also be used for all those diseases employing this mechanism.

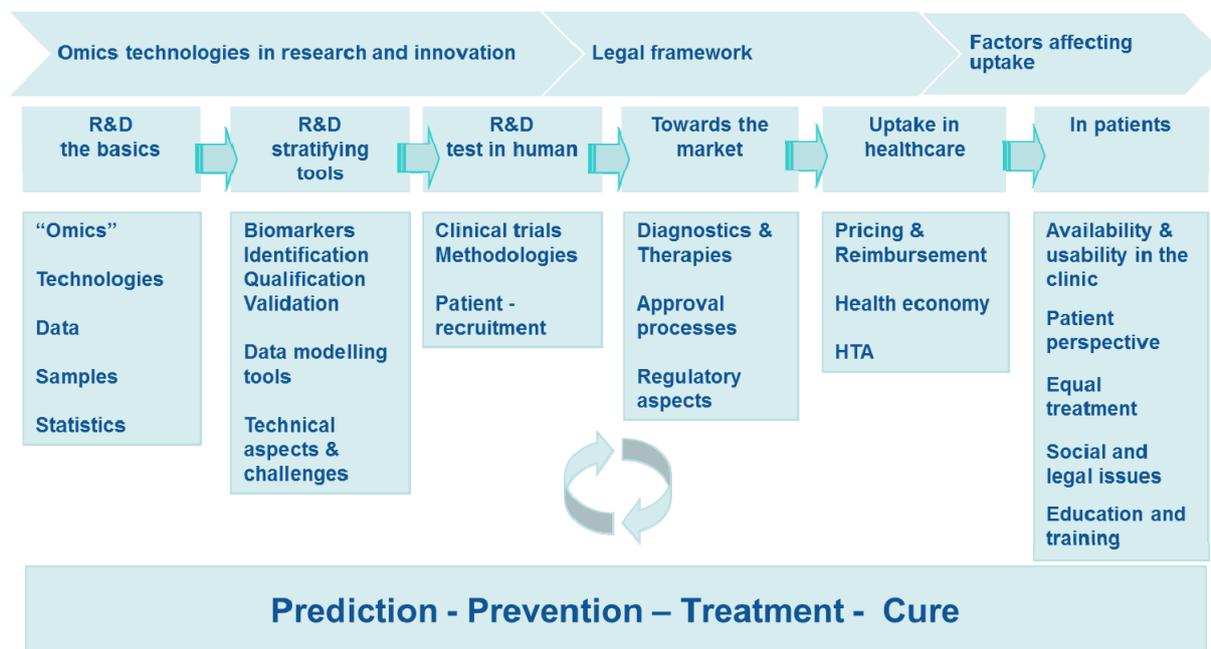
Equally important, the implementation of personalised medicine in the health care system will call for a steep increase in the number of screenings or diagnostic tests performed and a larger volume of data to be gathered, analysed and translated into information to serve as guidance for clinical decisions. Significant upfront investment may be needed for technological upgrades, structural changes, and education and training efforts for staff in health care systems. Such investment may however be offset by savings in unnecessary costs due to inadequate treatment for a patient. The economic impact of personalised medicine therefore needs to be considered from an overarching level, the so-called "societal" cost perspective encompassing the complete health care system as well as patient benefits in terms of reduced days of incapacity, days of hospitalisation, etc.

In addition, the current paradigm where the highest ‘value’ is attributed to therapies rather than to diagnostics may need to be revisited to ensure that high-quality diagnostics are also valued appropriately. Such a shift would be expected to speed up innovation in the area of personalised medicine. In this context, new incentive structures and models such as public-private partnerships for sharing the cost of new treatment strategies could be explored.

³ A biomarker: is an indicator of a biological state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers can be used both in the medicine development process and for diagnostic, prognostic, monitoring and screening purposes. See also section 3.2.

⁴ Based on figure from the UK, Human Genomics Strategy Group Building on our inheritance: Genomic technology in healthcare (2012)
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213705/dh_132382.pdf

While personalised medicine presents many opportunities for treating patients, several challenges to its implementation have also been identified. These challenges are present across what could be called the medical innovation cycle all the way from "bench to bedside", or in other words, from basic research to the uptake in health care. This cycle is shown in the schematic figure below⁵.



The figure is instructive as it shows that a holistic approach is needed to fully appreciate the challenges and opportunities presented by personalised medicine. Many of the challenges need to be addressed by research, which is why the European Commission organised the conference *European Perspectives in Personalised Medicine* in May 2011 to explore the most urgent areas for action at European Union level. The challenges identified at the conference cover all stages of the medical innovation cycle (a compiled list of these challenges can be found in the Appendix). Many of the key terms under the boxes in the figure will be further explained below.

3. R&D: -OMICS TECHNOLOGIES — POTENTIAL AND ISSUES IN THE DEVELOPMENT OF PERSONALISED MEDICINE

3.1. Basic research

3.1.1. *Molecular understanding of disease and redefinition of disease taxonomy*

Current health care models are organ-, system- or disease-oriented. Personalised medicine is expected to bring about a change of paradigm by integrating large-scale molecular data with clinical data. This can in the long term lead to new molecular definitions of disease, adding to or replacing the current clinical definitions. A better understanding of the molecular basis of diseases, especially if combined with knowledge of the interplay between the environmental factors to which individuals are exposed and their genetic make-up, will allow a better characterisation of pathologies and selection of more suitable treatment strategies.

⁵ The report from the conference 'European Perspectives in Personalised medicine' is available at: http://ec.europa.eu/research/health/policy-issues-personalised-medicine_en.html.

At the same time, understanding disease on a molecular level is crucial in the search for biomarkers and new medicine targets. Systems approaches may help to improve decision making in pharmaceutical development and may represent a new paradigm in the search for biomarkers and new medicine targets. Because of the high costs and pressure to deliver new products, pharmaceutical companies are frequently reluctant to venture into innovative but risky medicine discovery efforts. This might be remedied by more efficient collaboration between academia, industry, hospitals and patients in the early stages of medicine discovery and development.

In order to better capitalise on the new and emerging tools, and due to demographic and economic pressures, future treatments should better address the underlying common molecular pathways in addition to the current clinical classifications, and should also better reflect the increase in co-morbidities in the ageing population.

3.1.2. -Omics data gathering and analysis

The deciphering of the human genome sequence has significantly helped our understanding of biological processes, but the information obtained needs to be considered in conjunction with analysis of the functions of many classes of biomolecules, especially proteins. -omics technologies can provide that information in a high-throughput manner, providing a global view of molecular and cellular processes that have an impact on health and disease. However, high-throughput technologies have largely been used as a research tool whereas they should be introduced in the clinics. The resulting data might then be used to guide therapeutic intervention.

3.1.3. Development of -omics technologies for research and clinical use

Of the several existing -omics platforms, those for the analysis of nucleic acids are the most developed and closest to clinical application. With the advances in genomics technologies in the last decade, the price for whole genome sequences has dropped significantly, and a further price decrease is expected in the coming years. Therefore, the use of genomic technologies in medicine is likely to grow. Similarly, other -omics platforms (genomics, transcriptomics, epigenomics, proteomics, metabolomics, lipidomics and others) will advance further and technologies now used mainly for research will be reaching the maturity needed to meet the requirements of clinical settings. In addition, new -omics technologies might be developed. However, before all these technologies can reliably contribute to clinical studies, adequate data quality needs to be ensured. This would entail enhancing validation practices and introducing strict quality metrics. Furthermore, novel algorithms and statistical methods need to be put in place for analysis of the multiple layers of -omics data and integration of data derived from complementary platforms. Modern mathematics, physics, computational and engineering tools should be used more efficiently, and -omics experts would need to work with clinicians and statisticians to maximise benefits in health care.

Modern research tools generate large quantities of data and the cost of data generation is already surpassed by the costs of data analysis and storage. In order to efficiently translate millions of analyses into clinically meaningful information, the introduction of common reporting standards is necessary. Database-related efforts should focus on improving the definitions of ontologies so that system-scale data and associated metadata can be understood, shared and compared efficiently. New types of professionals able to deal with 'big data' will have to join the public health services to ensure usability and interoperability of the information stored.

There is an increasing role for research infrastructures in fostering multidisciplinary research, maximising knowledge exchange between disciplines and facilitating access to diverse

technologies. However, the resources needed to support the development and expansion of such infrastructure are significant and, once it is set up, a mechanism for long-term maintenance should be put in place.

3.1.4. Biobanks, sampling and harmonisation of data

Research into molecular understanding of diseases will rely on access to high-quality biological samples collected in a standardised manner. Access is needed both to large-scale population cohorts with core phenotype information and to smaller-scale age- and disease-stratified collections that are coupled with a large quantity of omics- and imaging-based phenotype information. The reproducibility of the results of -omics platforms is to a great extent determined by the pre-analytical phase of sample handling. Knowledge and standards of best practice for sample procurement and processing must therefore be developed and disseminated.

The European Union has a historical strength in large epidemiological studies, but technology development and implementation is needed to better ascertain environmental exposure and dietary heterogeneity. There is a lack of information about the quality and quantity of biological samples of existing European cohorts and about the completeness and consistency of phenotype data. This type of information is required to arrive at informed decisions on whether to invest in Europe's historical cohorts or to establish new ones. Enrolment and follow-up in large epidemiological studies will be more cost-effective if embedded in existing health care delivery systems. Collaboration between existing and new cohorts across Europe is to be encouraged.

The integration of data-dense information from the different -omics platforms at individual and population levels is an essential step in the identification and validation of biomarkers. The challenges include the storage, handling and integration of large volumes of data, necessitating data standardisation, the introduction of innovative IT solutions and 'bridging' with data stored in electronic health records. Therefore, it is important to create and maintain new data distribution systems in collaboration with data archives such as the European Bioinformatics Institute, the European Genotype Archive and the Array Express archive of functional genomics data electronic health records.

Protection of donors' fundamental rights to private life and personal data is an issue of the utmost importance for research using sensitive data on individuals' health status and genomic profiles. A further challenge is that anonymisation is usually not possible because the donor must be traceable in order to link disease outcome with the molecular profile.

Sufficient harmonisation of data protection rules is necessary to allow safe cross-border transfers of data in large research collaborations. Access to data and materials is critical to the progress of science generally, but plays a particularly important role in stem cell science. There is a need to develop publicly available electronic hubs for accessing a range of relevant data linked to individual stem cell lines. Access to pluripotent stem cell lines and the information associated with them is critical to the progress of stem cell science, but simple notions of access are substantially complicated by shifting boundaries between what is considered information versus material, person versus artefact and private property versus the public domain.

3.2. Pre-clinical research

3.2.1. Biomarker identification

Biomarkers are biological or physical indicators that can be measured and evaluated objectively. They show specific traits or changes that are linked to a disease or a particular health condition. Biomarkers are employed in clinical practice to describe both normal and

pathological conditions. Single biomarkers or combinations of biomarkers may be used to assess or detect:

- a specific disease as early as possible — **diagnostic biomarkers**
- the risk of developing a disease — **susceptibility/risk biomarkers**
- the evolution of a disease (indolent vs aggressive) — **prognostic biomarkers** — but they can be predictive too
- the response to and toxicity of a given treatment — **predictive biomarkers**

or to

- substitute for a clinical endpoint (a trait that reflects a medical condition) — **surrogate biomarkers**

Over the years, there has been a growing interest in biological indicators of disease evolution, therapeutic effect and medicine-induced toxicity. Biomarkers are increasingly used in medicine development to select patients and to assess their response to new therapeutic interventions in terms of toxicity and efficacy. Progressively, predictive biomarkers are finding additional application in the stratification of patient groups according to their clinical response to a treatment. Such stratification is based on the identification of patients with shared ‘biological’ characteristics by using molecular, biochemical and imaging diagnostic testing. It is a vital concept for the development of personalised medicine, which aims to ensure optimal management for patients and achieve the best possible result in terms of risk assessment, prevention and treatment outcome.

Due to genetic causes of variation among individuals, genotyping, epigenetics, gene expression analysis and metabolomics are key elements in the emergence of personalised medicine. So far, the majority of biomarkers used in personalised medicine are pharmacogenomic biomarkers. But nine years after completion of the human genome sequence, they are still limited in number.

3.2.2. *Technical aspects and challenges*

Biomarkers used to stratify patient populations (stratification biomarkers) can be identified by several means in pre-clinical studies, epidemiological studies or clinical trials. Genomics and other -omics technologies have greatly contributed to the identification and development of biomarkers. However, genomic technologies have limitations (functional significance of genetic variants, false negatives, etc.) and cannot encompass all approaches for the development of stratification biomarkers. A multiple approach integrating various technologies (-omics, phenotype studies, imaging, functional *in vivo* studies, etc.) needs to be pursued. Then the challenge is to deal with the generation of large amounts of complex data generated by -omics, phenotyping and imaging technologies. This requires the implementation of new statistical methods to cope with multi-signal assays. In addition, the identification of biomarkers relies heavily on data analysis, and the amount of medically relevant data available electronically is increasing dramatically. The challenge is to organise electronic data and to make them usable for research. The development of tests for biomarkers also requires access to biological resources where samples are carefully processed, stored and documented. Initial recommendations on samples and data handling are covered in the ICH⁶

⁶ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Topic E15 Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002880.pdf

and European Medicines Agency (EMA) guideline and the EMA reflection paper⁷ and are intended to provide key principles without imposing an unnecessary burden on small research entities. Development of standardisation is necessary.

Pre-clinical identification of stratification biomarkers combines an understanding of disease and medicine mechanisms and the unique characteristics of the individual. Ideally, it should be done as early as possible in medicine research and development. In practice, though, signatures that predict toxicity or efficacy can be identified afterwards, using information retrospectively. Such retrospective analyses are often criticised for being flawed by confounding factors and potential bias in patient selection. However, there are examples of well-designed retrospective analyses that have identified effective treatments for biomarker-defined subgroups of patients (mutations in the KRAS cancer gene associated with treatment failures). Hence, flexible paradigms could be considered where clinical trial designs could be adapted to the emergence of new data.

3.3. Clinical research

3.3.1. Biomarker qualification and validation

An increasing number of biomarkers are being discovered. But they cannot be used in clinics or in medicine development if they do not meet validation criteria. In this respect, a distinction is made between clinical qualification and validation.

Qualification is defined as ‘a conclusion that the biomarker data submitted support use of the biomarker in medicine research, medicine development or post approval studies and, where appropriate, in regulatory decision making’ (ICH E-16). The concept of qualification is dynamic and evolving. It takes into account the context and the intended use. The EMA’s Committee for Medicinal Products for Human Use delivers opinions and advice on request.

While qualification links a biomarker to a biological process or a clinical endpoint, validation includes assessment of the analytical method. So, the applicability of a qualified biomarker, i.e. its validation, also relies on the development of a robust and appropriate assay. In personalised medicine, the stratification assay accompanying the choice of therapy is called the ‘companion diagnostic test’. Qualification and validation processes, as well as clinical and laboratory procedures, are fundamental issues for the development of proper companion diagnostic tests (tissue collection, standardisation of technologies, prospective clinical trials, etc.). Standards for companion diagnostic tests are not so well established. However, specific requirements have been identified:

- High analytical validity;
- Appropriate sensitivity and specificity;
- Clinical validity/ Clinical utility;
- Ability to influence treatment plan;
- Ethical and social acceptance.

3.3.2. Clinical trial methodologies

Clinical trials are conducted in medical research and medicine development to allow statistically sound safety and efficacy data to be collected for health interventions. The current ‘gold standard’ is the randomised (double blind) controlled trial design, which has methodological advantages but does not always reflect clinical practice and concerns. Such

⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf.

trials are expensive and long undertakings and cannot always ensure timely availability to patients. A range of new, more flexible alternative designs, statistical methods and analysis tools need to be considered, for example: adaptive trial designs, which are computationally and logistically complex and need intensive modelling and simulation; enrichment designs, when sound biomarkers can accelerate the clinical development of personalised medicine meant to address unmet needs; Bayesian statistical approaches, which take better account of the available information; or well-conducted observational studies allowing the incorporation of actual experience in care settings. Strategies for adapting the clinical trials to allow fast availability of new medicines to patients and to incorporate effectiveness parameters are being explored to promote personalised medicine attuned to public health needs and constraints.

Trials can be considerably simpler, shorter and more efficient if the expected clinical readout is rapid. New or existing biomarkers can largely help, for example as (faster) surrogate end points.

To promote the contribution of genomics to the efficient development of new and personalised medicines, the EMA has developed scientific guidelines addressing the need to collect genomic samples throughout the development of medicinal products from early pharmacology studies, through pivotal clinical trials, up to post-authorisation experience⁸.

4. EU POLICIES AND LEGISLATION RELEVANT TO THE DEVELOPMENT OF PERSONALISED MEDICINE

4.1. EU research funding

4.1.1. Current research funding in FP7

Through the Seventh EU Framework Programme for Research and Technological Development (FP7), the European Commission has invested considerable funding in collaborative health research enabling or underpinning personalised medicine approaches. Since 2010, the FP7 calls for proposals have included personalised medicine as one of the research priorities and a number of topics have made specific reference to personalised medicine approaches, showing the importance attached to the area. The European Commission is also leveraging funding in health research contributing to personalised medicine through its international collaborations with other funders and through the Innovative Medicines Initiative, the public-private partnership with the European research-based biopharmaceutical industry.

4.1.1.1. Collaborative health research

It can be estimated that over EUR 1 billion⁹ of EU funding has been committed to research of interest to the advancement of personalised medicine in the fields of *tools and technologies for high throughput research, new diagnostics development* and *large-scale data gathering*, in particular for -omics research such as genomics, proteomics, metagenomics and epigenomics. As an example, a topic in the field of large-scale data gathering on *proteins and their interactions in health and disease*¹⁰ invited project proposals to gather a large amount of data on proteins relevant to human health and disease and their interactions in order to obtain an integrated view of biological processes. The aim of this research was to integrate proteomics, interactomics, structural biology and cell biology communities to provide a better overall understanding of cellular processes, building the necessary knowledge base for personalised

⁸ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid=WC0b01ac058002958e.

⁹ Estimation for EU-funded projects launched during the period 2007-2012.

¹⁰ Topic HEALTH.2011.2.1.1-2.

medicine. In the area of technology development, a topic on *development of technologies with a view to patient group stratification for personalised medicine applications*¹¹ was launched in order to support research and development and/or provide proof of principle of technologies for application in the area of personalised medicine.

Personalised medicine approaches in specific disease areas such as cancer, cardiovascular diseases and central nervous system diseases have also received EU funding. Several topics have aimed to develop generic tools and knowledge that will have a direct impact on the progress of the field.

In cancer, a topic on *predicting individual response and resistance to cancer therapy*¹² aimed to obtain validated risk stratification criteria for use in personalised, early and innovative patient screening methodologies, prediction of individual therapy response and resistance, and monitoring successful treatment outcome. The object of the research was to integrate relevant clinical data obtained through standardised methodologies such as pharmacogenetics, genomics and proteomics. In addition, currently ongoing projects in breast, colorectal, adrenal, renal and lung cancer use stratification and personalised medicine approaches in their research.

In the area of cardiovascular diseases, a topic on *evaluation and validation studies of clinically useful biomarkers in prevention and management of cardiovascular diseases*¹³ focused on the exploitation of existing and emerging biomarkers and related mechanisms to improve identification, risk assessment, clinical decision making and clinical outcomes and to contribute to the development of personalised and predictive medicine.

In the most recent FP7 calls, there has been a specific focus on rare disease research as a model to study personalised medicine approaches. The particularities of this area, such as small patient populations and predominantly genetic causes, make it an interesting case for investigating personalised medicine approaches. This is illustrated by the topic *-omics for rare diseases*¹⁴, which focused on constructing a solid foundation for the molecular characterisation of rare diseases through systematic application of -omics approaches and technologies and development of clinical bioinformatics linking the identified molecular profiles with current clinical descriptions. Topics on the *development of imaging technologies for therapeutic interventions in rare diseases*¹⁵ and *clinical trial methodologies for small patient populations*¹⁶ in particular for rare diseases or personalised medicine, have also been subject to funding in recent FP7 health calls. In addition, topics on *new methodologies for health technology assessment* and *comparative effectiveness research in health systems and health services interventions* have focused on the need to better understand the value proposition of personalised medicine and the implications of its application in health care.

The European Commission is also currently participating in several international programme level cooperation initiatives. These collaborations take the form of international consortia in which member organisations work towards common goals and objectives while using their own funding mechanisms and rules. Working together with other funders and organisations investing in research has a number of advantages, such as the ability to maximise resources and enhance research capacities, reduce potential research overlaps, tackle more ambitious

¹¹ Topic HEALTH.2012.1.2-1.

¹² Topic HEALTH.2010.2.4.1-8.

¹³ Topic HEALTH.2011.2.4.2-2.

¹⁴ Topics in the area HEALTH.2012.2.1.1-1.

¹⁵ Topic HEALTH.2013.1.2-1.

¹⁶ Topic HEALTH.2013.4.2-3.

research goals based on societal needs, and promote common quality standards and open access and data sharing policies

4.1.1.2. International collaboration relevant to -omics research

The European Commission has actively participated in the launch of five international consortia with a relevance to -omics research since the year 2007¹⁷, namely: the International Knock Out Mouse Consortium, the International Human Microbiome Consortium, the International Cancer Genome Consortium, the International Human Epigenome Consortium, and the International Rare Diseases Research Consortium. EU collaborative projects have been funded under each initiative to contribute to the overall goals of the consortia, including one ‘high impact’ project with a budget of EUR 30 million in the area of epigenetics. The international consortium model allows members to come together to identify common standards and research priorities while at the same time coordinating research to avoid overlaps and create critical mass.

For example, the primary goals of the International Cancer Genome Consortium (ICGC) are to generate comprehensive catalogues of genomic abnormalities (somatic mutations, abnormal expression of genes, epigenetic modifications) in tumours from 50 different cancer types and/or subtypes that are of clinical and societal importance across the globe, to make the data available to the entire research community as rapidly as possible, with minimal restrictions, and to accelerate research into the causes and control of cancer.

4.1.1.3. The Innovative Medicines Initiative

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is one of five Joint Technology Initiatives (JTI) set up under FP7. These initiatives were launched in order to create new partnerships between publicly and privately funded organisations involved in research, focusing on areas where research and technological development can contribute to European competitiveness and quality of life. The JTIs have been instrumental in promoting industry-driven research with the aim of establishing European leadership in certain technologies that are strategic to the future of the European Union.

Through IMI JU, the European Commission is partnering with the European Federation of Pharmaceutical Industries and Associations (EFPIA) to fund research aiming to overcome bottlenecks in pharmaceutical R&D. The ultimate goal is to provide effective and safer medicines for patients. The European Commission contributes EUR 1 billion to the IMI research programme, an amount matched by mainly in-kind contributions (consisting mostly of research activities) worth at least another EUR 1 billion from EFPIA member companies. Research consortia funded under IMI team up academic research groups, patient organisations and SMEs with the pharmaceutical companies that are members of EFPIA.

IMI JU’s research programme is dedicated to pre-competitive biopharmaceutical research on the safety and efficacy of medicines as well as knowledge management, and education and training. The IMI projects have already delivered significant results in areas such as schizophrenia, asthma, cancer, diabetes, chronic pain and lung disease. Many of the projects currently funded under IMI JU are directly contributing to the development of personalised medicine approaches through the use and development of -omics technologies. For example, the DIRECT project aims to develop a stratified medicines approach to the treatment of type 2 diabetes with either existing or novel therapies and the U-BIOPRED project focuses on

¹⁷ http://ec.europa.eu/research/health/large-scale/omics/international-initiatives-disease-genomics_en.html

speeding up the development of better treatments for patients with severe asthma by developing innovative testing methods to classify patients into distinct severe asthma types¹⁸.

In addition to the FP7 health theme of the Cooperation programme, other areas under FP7 contribute to advancing the knowledge and understanding of personalised medicine, such as research on ICT technology for health and research infrastructures.

4.1.2. Horizon 2020 outlook

The next EU framework programme for research and development for the period 2014-2020 is called Horizon 2020 and has a budget of some EUR 70 billion. It will combine all research and innovation funding currently provided through the [Framework Programmes for Research and Technological Development](#), the innovation related activities of the Competitiveness and Innovation Framework Programme (CIP) and the European Institute of Innovation and Technology (EIT). Gathering all funding instruments under the same programme represents a novelty in EU research funding.

The Commission's proposal has a focus on societal challenges that should allow a higher degree of integration of different fields of research. This approach will cover activities from research to the market in an effort to bridge the current gap between the two. In this respect, *the Health, Demographic Change and Wellbeing Challenge* fits well the need for a multidisciplinary approach to the field of personalised medicine which is essential to move the area forward. Thus, under the current proposal, personalised medicine will continue to be one of the research priorities as advances in the area will demand further fundamental as well as applied research, including the integration of various sources of data.

There are also plans to continue the partnership with the pharmaceutical industry under a collaborative framework similar to the current IMI. "IMI 2" is proposed to have an enlarged scope aiming to provide favourable conditions for translational research in the European life sciences sectors. The continued collaboration should create further incentives for industry investment in research on personalised medicine.

Challenges and opportunities¹⁹

The EU research programme offered opportunities of funding projects with over EUR 1 billion of EU funding for the period 2007-2012. This ensured research of interest to the advancement of personalised medicine.

Some of the most important challenges in research that will inform the calls of proposal under Horizon 2020 can be summarised under the following four areas:

- *Breaking barriers and speaking the same language:* Facilitating interaction between different disciplines from basic to clinical research by creating appropriate interfaces for collaboration and discussion among stakeholders.
- *Generating knowledge and developing the right tools:* Adapting research tools to clinical use by developing common standards for example data collection and linking clinical data with molecular profiles; translating -omics research into clinical application.
- *Translation into medical applications:* Finding new approaches for the identification, qualification and clinical validation of all types of biomarkers; improving the use of biomarkers for better use of existing therapies and adaptive clinical trial methodologies.

¹⁸ Read more about both projects on: <http://www.imi.europa.eu/content/ongoing-projects>.

¹⁹ Based on outcome of conference European Perspectives in Personalised Medicine, 2011.

- *Economic aspects*: Proving the economic viability and positive patient benefits of personalised medicine and developing methodologies for health technology assessment (HTA) and for comparative cost-effectiveness studies of personalised medicine approaches.

4.2. Regulatory framework

While medicinal products and the screening of genomic characteristics with diagnostic tests are closely inter-linked in personalised medicine, the current EU regulatory frameworks for the marketing of medicinal products and the corresponding diagnostic medical devices are different. Medicinal products administered to the patient fall under the regulatory framework for medicinal products while diagnostics as such are covered by the legislation governing *in vitro* diagnostic medical devices. While the different pathways are justified by the different nature of the products, both frameworks aim to ensure a high level of public health protection and to promote the functioning of the internal market, with measures which moreover encourage innovation.

4.2.1. *In vitro* diagnostic medical devices

In vitro diagnostic medical devices (IVDs) are products used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body.

Such devices must comply with the essential requirements set out in Directive 98/79/EC (IVD Directive)²⁰ to ensure a high standard of safety and performance when they are placed on the market. To ensure such compliance, the devices need to undergo an appropriate conformity assessment. Since the large majority of such devices do not constitute a direct risk to patients and are used by trained professionals, the general rule is that the conformity assessment can be carried out under the sole responsibility of the manufacturer. The intervention of ‘notified bodies’ is needed only for specific devices where correct performance is essential to medical practice and failure can cause a serious risk to health. Such devices include, for example, products used in blood transfusion. The involvement of a notified body is also required for devices for self-testing.

The manufacturer can then affix the CE mark on its products to demonstrate that they comply with the essential requirements of the IVD Directive. If an IVD is CE marked, it does not need any additional approval or certification to be marketed in the entire EU, the European Economic Area (EEA), Turkey and Switzerland.

The recently proposed revision of the IVD Directive²¹ aims to strengthen some key aspects of the IVD system, for instance oversight by notified bodies, post-market safety, transparency, traceability and the overall regulatory management of the system. It also offers the opportunity to eliminate the gaps and weaknesses of the IVD Directive so as to ensure that IVDs used in the context of personalised medicine offer the appropriate level of safety and performance.

During the public consultation on the revision, a majority of stakeholders supported the view that diagnostic medical devices used in the field of personalised medicines should continue to be regulated under the IVD legislation. Therefore, a key improvement in the Commission’s proposal for a Regulation on *in vitro* diagnostic medical devices is the explicit inclusion of diagnostics used in the context of personalised medicine in the definition of an IVD.

The fact that most diagnostic medical devices are currently self-certified by the IVD manufacturers has prompted the question whether the present regime ensures they have a

²⁰ Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices, OJ L 331, 7.12.1998.

²¹ COM(2012) 541 final.

sufficient level of safety and performance when placed on the market. For this reason, the Commission proposal calls for the adoption of a more robust risk-based classification system for diagnostics. If this classification system is adopted, the placing on the market of diagnostics used in the field of personalised medicine will systematically involve a notified body in the conformity assessment procedure. This will contribute to ensuring that only safe and high-quality diagnostics are put on the EU market.

Genetic tests required for the prescription of omics-based medicines are often carried out by laboratories. Currently, the IVD Directive excludes from its scope ‘devices manufactured and used only within the same health institution and on the premises of their manufacture or used in premises in the immediate vicinity without having been transferred to another legal entity’. Therefore, the tests that laboratories manufacture and use themselves fall under national laws. This exemption has come under criticism since it does not ensure a uniform high level of safety and performance for ‘in-house’ tests across Europe. In its proposal, the Commission proposes to limit the exemption for lower-risk IVDs by making it subject to two conditions: first, manufacture and use must occur solely under the health institution’s single quality management system, and, second, the health institution must be compliant with standard EN ISO 15189 or any other equivalent recognised standard. High-risk ‘in-house’ tests would be subject to all the requirements of the proposal, except for the provisions on CE marking and the registration obligations. This is of particular importance in order to prepare for the anticipated extensive use of -omics testing platforms within the public health system not only for selection of the most appropriate medicines but also for public health research, disease prevention and risk factor management.

Finally, for companion diagnostics intended to assess patient eligibility for treatment with a specific medicinal product, the proposal provides for a consultation procedure with the EMA or one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC in the context of the conformity assessment procedure for the companion diagnostic. The consultation will concern the suitability of the companion diagnostic in relation to the safe and effective use of the medicinal product in question.

4.2.2. *Medicinal products*

4.2.2.1. Authorisation

No medicinal product may be placed on the market in the EU without a marketing authorisation. Medicinal products have to comply with the requirements of EU pharmaceutical legislation²². The legislation includes detailed rules on the requirements and procedures for obtaining marketing authorisation, coupled with a system of continuous monitoring of already authorised products on the market through pharmacovigilance. This system allows subsequent decisions to be taken to amend marketing authorisations or remove products with an unfavourable benefit/risk profile from the market. While not containing specific provisions on personalised medicines, the legislation also covers medicinal products making use of -omics technologies.

²² Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, as amended.
Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, as amended.

In order to obtain a marketing authorisation from the competent authority in the Member States or the European Commission²³, the medicinal product has to demonstrate a positive benefit/risk balance based on the assessment of its safety, efficacy and quality. To demonstrate this, the dossier for an application for marketing authorisation of an innovative medicinal product should include, amongst other information, the results of pharmaceutical tests, pre-clinical (toxicological and pharmacological) data and clinical data in conformity with the EU pharmaceutical legislation.

With a view to meeting unmet medical needs of patients and in the interests of public health, EU pharmaceutical legislation provides the possibility for granting ‘conditional marketing authorisations’ on the basis of less complete data than is normally the case and subject to specific conditions and obligations. Such authorisations might be particularly needed when the patient population in a disease is small and comprehensive clinical trials are not feasible or where the medicinal product aims at the treatment, the prevention or the medical diagnosis of seriously debilitating or life threatening disease. A conditional marketing authorisation may be granted provided that the benefit/risk profile is positive, the benefits to public health of making the medicinal product concerned available immediately outweigh the risks inherent in the fact that additional data are still required, and these data will be provided and assessed later. The new pharmacovigilance legislation in this respect provides additional tools for the conduct of post-authorisation safety and efficacy studies. Conditional marketing authorisations are valid for one year on a renewal basis.

Once the specific obligations are fulfilled and the missing data are provided, it is possible to convert the conditional marketing authorisation into a normal marketing authorisation.

In exceptional circumstances, when the applicant can show that he is unable to provide comprehensive data on efficacy and safety of the medicine under normal conditions of use e.g. when the indications for which the medicine is intended are so rare that the applicant cannot reasonably be expected to provide comprehensive evidence, a marketing authorisation under ‘exceptional circumstances’ may be granted subject to specific conditions. Continuation of the marketing authorisation is linked to an annual reassessment of the conditions.

4.2.2.2. Clinical trials

The results of clinical trials are of key importance to demonstrate that medicines are safe and effective before being placed on the market. The pharmaceutical legislation defines a clinical trial as *‘any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy’*.

²³ The European Commission authorises medicines through the centralised procedure, which is compulsory for products derived from biotechnology, for orphan medicinal products and for medicinal products for human use which contain an active substance authorised in the Community after 20 May 2004 and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes. The centralised procedure is also mandatory for veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth or to increase yields from treated animals. Applications for the centralised procedure are made directly to the European Medicines Agency (EMA) and lead to the granting of a European marketing authorisation by the Commission which is valid in all Member States.

Clinical trials are an indispensable part of clinical research, both to develop new medicinal products and also to improve the use of or define new indications for medicinal products already authorised.

The current EU Clinical Trials Directive²⁴ aims to ensure that clinical trials are conducted in compliance with good clinical practice (GCP), a set of internationally recognised ethical and scientific quality requirements that must be observed for designing, conducting, recording and reporting clinical trials involving the participation of human subjects. Compliance with GCP provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

In order to boost clinical research in Europe, the Commission has adopted a proposal for a Regulation²⁵ replacing the current Directive.

This Regulation, once adopted, will greatly facilitate the conduct of clinical trials throughout Europe. This is crucial in particular for personalised medicines, where diseases are increasingly narrowly defined (i.e. linked to genetic characteristics). In order to reach recruitment targets, it is important to roll out the clinical trial over several (or even all) Member States.

Moreover, the Regulation, once adopted, will facilitate the conduct of clinical trials by non-commercial ('academic') sponsors, i.e. sponsors who conduct trials primarily for treatment optimisation and not with the aim of obtaining a marketing authorisation.

The proposed Regulation specifically provides for:

- An authorisation procedure for clinical trials to allow for fast and thorough assessment of the application by all Member States concerned and ensure a single assessment outcome.
- Simplified reporting procedures to spare researchers from submitting largely identical information on a clinical trial separately to various bodies and Member States.
- More transparency on whether recruitment for participation in a clinical trial is still ongoing, and on the results of the clinical trial. To enhance the knowledge basis and consequently innovation, a summary of the trial will have to be published on the database one year after the termination of each trial.

4.2.2.3. Pharmacovigilance

Clinical trials concluded prior to marketing authorisation cannot always detect rare adverse reactions or adverse reactions associated with long-term administration of a medicine in a large population. Continuous monitoring of the effects of a medicine is therefore important. Moreover, the possibility offered in the recently revised EU legislation on pharmacovigilance for patients to directly report on adverse events is expected to further facilitate the integration of pharmacogenomic data into medical care. Adverse reaction reporting could facilitate the development of a knowledge base. Such information could be useful for further product development, and could be used to monitor and extend the benefits of the clinical use of personalised genome-based medicines. To this end, the EMA is developing guidelines for the use of genomic methodologies in pharmacovigilance, based on the experience gained in clinical development and in the clinical use of medicinal products on the market. This will

²⁴ 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

²⁵ COM(2012) 369 final.

lead to the identification of genomics biomarkers useful for ‘personalisation’ and the minimisation of serious adverse events, inappropriate co-medications and treatment failure (e.g. abacavir, phenytoin, carbamazepine, allopurinol²⁶, tamoxifen²⁷, etc.). The European medicines web portal established by the new pharmacovigilance legislation might become a new source of information in this regard, as the EMA will publish on this portal the protocols and abstracts of results of post-authorisation studies required from the marketing authorisation holder.

4.2.3. *Personal Data protection*

The Commission’s proposal for a General Data Protection Regulation²⁸, once adopted, will replace the current Directive 95/46/EC, which harmonises the national data protection laws. Following in the footsteps of the current Directive, the proposed Regulation prohibits the processing of special categories of personal data such as data concerning health (Article 8). This prohibition is only lifted in certain clearly defined circumstances [Article 8(2)]. That will be the case inter alia when processing of data concerning health is necessary for health purposes and subject to the specific conditions and safeguards laid down elsewhere in the proposed Regulation (Article 81) or when processing is necessary for historical, statistical and scientific research purposes subject to conditions and safeguards set out in a separate provision (Article 83).

According to the proposed Regulation, the processing of personal data concerning health may be necessary for certain reasons of public interest in the areas of public health (these reasons have been expressly defined in Article 81) without the consent of the individual concerned. It is in any event required that such processing must be based on EU law or Member State law and has to be accompanied by suitable and specific safeguards. The processing of data for scientific research purposes will need to comply with the conditions that will be specified in Article 83 of the future Regulation

The harmonisation of data protection requirements in the EU should also improve the industry’s ability to conduct meaningful biomedical research that leads to the discovery of new medicines, and should allow monitoring of the benefit/risk profile of medicines for public health.

4.2.3.1. *Data exclusivity and market protection*

Placing a medicine on the market is associated with high costs for developing the product and generating pre-clinical and clinical data to demonstrate its efficacy and safety. Therefore, EU pharmaceutical legislation provides for two main types of regulatory incentives to promote innovation by giving innovative industry the possibility to recoup its investment in the often lengthy and costly development of new innovative medicines²⁹: data exclusivity and market protection. An innovating company has eight years of ‘data exclusivity’, during which their pre-clinical and clinical trial data may not be referenced in the marketing authorisation dossier of another company (generic company) for the same active substance. In addition, generic

²⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/07/WC500130391.pdf.

²⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097444.pdf.

²⁸ COM(2012) 11 final.

²⁹ Costs for the pharmaceutical industry of bringing a new innovative medicine to the market are subject to a variety of estimations. Industry estimations collected for the Commission pharmaceutical sector inquiry varied between US\$ 450 million and 800 million, or US\$ 1 billion if the cost of failed projects were included. For biopharmaceuticals, the costs were generally reported to be higher than those of ‘traditional’ pharmaceuticals. These estimations did not address specifically personalised medicine; the development of such medicine can be considered as highly innovative and complex, as it requires expertise in different technological and scientific fields.

products may not be placed on the market until ten years after the initial authorisation of the innovative product (=market protection).

An additional year of market protection (i.e. 8 + 2 + 1) is added if, during the first eight of the ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications considered to bring a significant clinical benefit³⁰.

4.2.3.2. Patents³¹

The above mentioned data exclusivity and market protection incentives are separate from the possibility to protect inventions by patent. Patents provide an incentive for companies to make the necessary investment in research and innovation by giving the owner the right to prevent others from making, using or selling the invention without its permission.

Today, (technical) inventions can be protected in Europe either by national patents granted by the competent national authorities or by 'classical' European patents granted centrally by the European Patent Office. Once the international agreement on the Unified Patent Court has entered into force and the two Regulations³² for the creation of unitary patent protection are applicable, it will be possible to obtain a European patent with unitary effect. Such a patent will in principle provide uniform protection for 25 Member States (all Member States but Italy and Spain)³³ on the basis of one application and without additional validation and translation requirements in the individual Member States, thus providing huge cost advantages and reducing administrative burdens. In addition, the Unified Patent Court, a specialised jurisdiction in patent matters for the participating Member States, will help enhance legal certainty for business and avoid duplication/multiplication of litigation cases before the various courts of the Member States concerned.

The development of pharmaceuticals is a time-consuming process with a high R&D expenditure. Patent protection is essential in order to recoup the R&D investment. However, before pharmaceuticals can be marketed, they must undergo a mandatory approval procedure in order to demonstrate their safety and efficacy. By the time the product is marketed, parts of the patent term have often expired. In order to compensate the patent owner for this loss of effective patent protection, a system of supplementary protection certificates (SPCs) has been established for medicinal products. SPCs prolong the protection of pharmaceutical patents by up to five years.

³⁰ Moreover, when an application is made for a new indication for a well-established substance, a non-cumulative period of data exclusivity is granted, provided that significant pre-clinical or clinical studies were carried out for the new indication (Article 10(5)). Furthermore, when a product is switched from a prescription medicine to a non-prescription product and this change of classification has been authorised on the basis of significant pre-clinical tests or clinical trials, it enjoys another year of data exclusivity for these data (Article 74a).

³¹ A patent is a legal title that can be granted for any invention having a technical character provided that it is new, involves an inventive step and is susceptible of industrial application. A patent gives the owner the right to prevent others from making, using or selling the invention without permission. The unitary effect of a European patent, which is registered in Register for Unitary Patent Protection, is limited to those Member States where the Unified Patent Court has exclusive jurisdiction at the date of registration.

³² Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection, OJ L 361, 31.12.2012.

Council Regulation (EU) No 1260/2012 of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection with regard to the applicable translation arrangements, OJ L 361, 31.12.2012.

³³ Agreement preceded the accession of Croatia.

4.2.3.3. Incentives offered by ‘orphan’ designation

Regulation (EC) No 141/2000 on orphan medicinal products, which provides incentives for the research and development of medicines mainly for life-threatening and rare diseases, has triggered considerable innovation in this area as well. While the benefits offered by this Regulation depend on the fulfilment of its specific designation criteria, an increasing number of products based on a ‘personalised approach’ have been designated as orphan medicinal products (e.g. based on the use of autologous cells) and are currently under development for marketing authorisation³⁴. An increasing number of ‘stratified medicines’ involving -omics technologies have been authorised for use in selected populations for orphan conditions such as cystic fibrosis or genetic inherited enzyme deficiency. Companies with an orphan designation for a medicinal product benefit from incentives such as scientific assistance, fee waivers and ten years of market exclusivity after authorisation.

In 2012, the European Union provided EUR 7,49 million for companies of orphan medicines to receive reductions in the regulatory fees payable to the EMA.

Table 1 : Overview of fee reduction types processed in 2012 (in EUR)

Protocol Assistance (including follow-up)	4 502 050
Initial Marketing Authorisation	2 204 370
Inspections	494 100
Variations	106 100
Annual fees	184 100
Total	7 490 720

Orphan medicines have other similarities with personalised medicine, such as high costs for R&D, small target populations, or extensive education required for physicians. Consequently, this may raise affordability issues from the perspective of payers (public health systems and/or private insurers).

4.2.3.4. Incentives for paediatric medicinal products

For paediatric medicinal products, the validity of the supplementary protection certificate can be extended by six months under specific conditions. In addition, medicines developed specifically for paediatric use and with an age-appropriate formulation can also obtain a paediatric use marketing authorisation, offering ten years of data and market exclusivity. For orphan medicines for children, the legislation provides an additional two years of market exclusivity on top of the existing ten years under the EU’s Orphan Regulation.

4.2.3.5. Other incentives for the development of medicinal products

The scientific committees of the EMA give scientific advice to companies for the development of medicinal products. Such advice is given case-by-case for a given product under development. Specific provisions in EU legislation³⁵ enable micro, small and medium-sized enterprises developing medicinal products to receive financial and administrative assistance from the EMA. In addition, the possibility of multi-stakeholder scientific advice, with the participation of regulators, patients’ organisations and health technology assessment

³⁴ By April 2011, this number was 26. At the time of orphan designation, most (81 %) of the applications contained data from clinical studies. The majority of active substances designated were either autologous cells or gene therapy products. Other active substances can be described as monoclonal antibodies, recombinant proteins and others (Source: EMA).

³⁵ Commission Regulation (EC) No 2049/2005.

experts, has recently been introduced for a number of highly innovative medicinal products in the development phase. Scientific advice has notably be given on products in development with specific questions on genomic biomarkers.

In order to facilitate the development of personalised medicine products, the EMA's Pharmacogenomics Working Party has produced a number of reflection papers and concept papers concerning pharmacogenomics in the development and evaluation of medicinal products³⁶. The group provides both valuable input and expertise in developing consistent information and guidelines for '-omics' personalised treatments (including medicines and their companion diagnostics). Another EMA key activity to support personalised medicine is the qualification of biomarkers beyond the procedure of processing individual market authorisation applications or giving scientific advice for the development of individual products³⁷. These scientific opinions, finalised after open consultation with the scientific community, are made available to the public and to sponsors (from academia and industry) in order to support and facilitate further innovative medicine development³⁸.

At international level, EMA and the US Food and Drug Administration (FDA) have concluded the first joint qualification process for biomarkers by qualifying the use of a number of biomarkers³⁹.

Moreover, to support medicine innovation in the EU, the EMA Task Force on Innovation (ITF) provides a scientific platform bringing together expertise in the areas of quality, safety, efficacy, pharmacovigilance, scientific advice, orphan medicinal products and good-practice compliance to advise companies in particular on *emerging therapies and technologies*⁴⁰.

4.2.4. Personalised medicines authorised so far

The European Commission consulted the Member States and EMA on the experience with personalised medicines authorised in the European Union. The experience of the EMA includes:

- Assessment of products approved under the centralised procedure⁴¹, for which predictive genomic biomarkers are to be measured before exposure to the treatment — Since 1999, at least 23 personalised medicines with safety or patient selection benefits based on genomic biomarkers have been authorised via the centralised procedure. It should be noted that around 10% of all products authorised via the centralised procedure have genomics biomarkers identified not only for therapeutic indications, but also for contraindications or posology instructions, thus having a major impact on the 'personalisation' of treatment beyond stratification. Submissions for the marketing authorisation of genomically targeted personalised medicines are gradually increasing.

³⁶ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958e

³⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf.

³⁸ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0#section2.

³⁹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000349.jsp&mid=WC0b01ac05800baedb.

⁴⁰ http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000339.jsp&mid=WC0b01ac05800baed8.

⁴¹ Authorisation granted by the European Commission after a scientific assessment conducted by the European Medicines Agency.

- Orphan medicinal products approved by the centralised procedure which follow the personalised medicine approach.

Likewise, some Member States (such as Ireland and Sweden) have authorised medicines at national level or through mutual recognition procedures, where:

- screening is recommended before exposure of patient to the treatment;
- screening is not recommended but information is given in the summary of the product characteristics.

The objective is to ensure the efficacy and safety of the medicines for patients.

Challenges and opportunities:

- The *revision of the medical device legislation* will explicitly include in the definition of IVD companion diagnostics used for personalised medicine and will strengthen the classification system for diagnostics and consequently the procedures for assessing them.
- A *better consultation process for companion diagnostics* intended to assess patient eligibility for treatment with a specific medicinal product will improve coordination of the regulation relating to pharmaceuticals and diagnostics.
- The *revision of the Clinical Trials Directive* will simplify the conduct of clinical trials across the EU.
- The current *patent reform* will provide cost advantages and reduce administrative burden.
- The reinforced *pharmacovigilance* system on medicinal products will be a new source of information on adverse reactions.
- The current *marketing authorisation procedure* and the existing *incentives* can accommodate and accelerate the placing on the market of medicines based on the personalised medicine approach.

5. FACTORS AFFECTING THE UPTAKE OF PERSONALISED MEDICINE IN HEALTH CARE

In a context of public budget deficits and an ageing population, public health budgets in the European Union⁴² are under considerable strain. Ever-increasing resources are required to treat diseases such as cancers, chronic or degenerative diseases and diabetes⁴³. In contrast with the great expectations for personalised medicine in offering savings for public health budgets through efficiency gains, fears have been expressed that targeted treatment options may put strains on public health care budgets⁴⁴.

The French Cancer Institute has shown that investing in molecular testing for the use of stratified and targeted medicines can in fact bring significant savings to the public health

⁴² Under the Treaty on the Functioning of the EU, the competence for the definition of health policies and for the organisation and delivery of health services and medical care lies with the Member States. In this context, Member States are also competent for decisions on pricing and reimbursement of medicinal products.

⁴³ EFPIA Disease burden in Europe (2009): each year over 2 million deaths in the EU are caused by cardiovascular disease and 1.4 million by cancer. 80 million people in Europe have some form of allergic disease and the number is increasing. Some 23 million people in Europe are diagnosed as having depression at any one time. Diabetes affects 246 million people worldwide and the number is expected to grow. Alzheimer's disease affects about 26 million people worldwide and the number is also expected to grow. Commission Staff Working Document-Mid-term evaluation of the Health Programme 2008-2013 (COM(2012)83)

⁴⁴ Communication COM(2008) 666 final.

sector, as the cost of testing is offset by the reduction in non-effective or inappropriate prescribing. However, there are not enough examples that personalised medicinal products are not only effective but also cost-effective. The experience from orphan medicinal products, i.e. products for small patient populations, shows that these products are often expensive. In the case of personalised medicine, the cost of diagnostic tests adds to the cost of the medicinal product.

A specific characteristic of personalised medicinal products is that, in addition to the need for prescribers of such medicines to have pharmacogenomic knowledge (requiring education and training), they also need to have adequate IT tools and systems at their disposal. Doctors will need to be trained in a number of disciplines in order to understand and to be able to use all the sophisticated tools that will be at their disposal for personalised medicine. And once trained, they should have access to diagnostic and treatment facilities to administer this care in line with the EU principle of health equality and universal access to medicine. This is a further challenge for national health systems.

The effective uptake of personalised medicine approaches in a Member State will depend on acceptance of the medicinal products and the diagnostic tests by the payers, the public health care system and private health insurance. Both medicinal products and diagnostic tests, even if already authorised to be placed on the market, may thus be subject to rigorous evaluations of their cost and clinical effectiveness in comparison with other therapies available to treat the same disease.

The development of personalised medicine will have some impact, not yet assessed, on the pharmaceutical industry (R&D pipeline prioritisation, pricing policies), healthcare professionals (training needs, skills profiles, etc.), patients (affordability and equity issues), and health systems (affordability issues, infrastructure needs, etc.). Availability of prognostic testing may further increase the challenges in designing the appropriate funding models for health systems.

5.1. Health Technology Assessment

Evaluations of impact are already to some extent carried out under a health technology assessment (HTA). The use of HTA has increased in European countries over the last decades, as it has proved to be a useful tool for providing a transparent, non-biased basis for decisions on the uptake of new medicines, medical devices, surgical procedures and other health interventions.

The work of HTA agencies can be different in volume and scope depending on their mandate in the individual Member State. The following table summarises the "Applied criteria for HTA in selected European countries" (Sorenson et al, 2008).

Criteria	AT	BE	CH	DE	FI	FR	NL	NO	SE	UK
Therapeutic benefit	X	X	X	X	X	X	X	X	X	X
Patient benefit	X	X	X	X	X	X	X	X	X	X
Cost-effectiveness	X	X			X		X	X	X	X
Budget impact		X			X	X	X	X		X
Innovative characteristics	X					X	X			X
Availability of therapeutic alternatives	X	X					X		X	X
Equity considerations		X				X		X	X	X
Public health impact						X				
R&D					X					

As illustrated in the table, all agencies consider first the clinical domains such as the therapeutic benefit and the patient benefit (including quality of life).

HTA assesses aspects such as cost-effectiveness and budget impact as well as patient outcome, safety, organisational, legal, ethical and societal aspects. It can include an evaluation of the therapeutic benefits and economic impacts of the product for patients and society as a whole. As regards personalised medicine, the cost of patient screening/diagnosis is weighed against the savings made by avoiding unnecessary and inadequate use of ‘one-size-fits-all’ medicinal products and the additional time and expense treating adverse reactions⁴⁵.

A successful HTA evaluation of personalised medicine requires the HTA methods to take into account the specificities of the technologies involved and to adopt a long-term and societal view of the benefits of such medicine. A recent study of a model for evaluating the economic impact of personalised medicine for breast cancer patients, based on real data from hospitals in Belgium and the UK, indicates potential savings. This study showed a 37% reduction in total patient costs for health care without affecting the average QALY (quality adjusted life years)⁴⁶. However, this saving is only achievable with upfront investment in diagnostic techniques and electronic health records, which was not included in the cost analysis.

Evidence from European HTA agencies illustrate that so far very few medicinal products based on this approach have emerged. The issue has been raised particularly with regard to so-called companion diagnostics, which can be - and have been - included in technology appraisals for new medicinal products.

For example, the National Institute for Health and Clinical Excellence (NICE) in the UK has published 134 appraisals of health technologies since 2006. Of these, 47 concern diagnostic tests, but only five involve companion diagnostics. The majority of diagnostic tests appraised concern disease severity assessment, followed by imaging tests, protein expression and a few genetic tests. The five companion diagnostics all relate to the treatment of cancer.

5.2. Methodological issues in HTA

Although the examples so far are few, the HTA agencies already see some important methodological challenges in assessing companion diagnostics type health care product.

⁴⁵ See, for example, Impact of pharmacogenomics on health care and health economics, International Journal of Pharmaceutical Medicine 15, 95-100 (2001).

⁴⁶ [http://www.healthpolicyandtechnology.org/article/S2211-8837\(12\)00044-5/abstract](http://www.healthpolicyandtechnology.org/article/S2211-8837(12)00044-5/abstract).

For example, there is so far no established ‘HTA gold standard’ for assessing diagnostic tools. Without this, both industry and HTA agencies struggle to sufficiently demonstrate the accuracy of the tests and thereby their effectiveness.

The use of *post hoc subgroups* as a basis for identifying the relevant marker for the diagnostic test is also a challenge.

In HTA, the *relative effectiveness* of a given treatment (compared to other treatments) is an important element. However, relevant comparator data may not be generated in the same clinical trial, and will thus usually not be available for the specific target population in question. Moreover, the availability of the test may be an issue.

Another issue is whether the test in question is the most accurate to identify the marker. This has major consequences for assessing the effectiveness of the medicinal product associated with the diagnostic tool. A sub-optimal test may lead to incorrect estimation of the effectiveness of the medicine, which in turn may give rise to a wrong recommendation on use. Therefore, every time a better diagnostic tool is developed, the effectiveness of the associated medicinal product should in principle be re-assessed.

Because personalised medicines represent often ‘break-through’ treatment, competent authority requires further input from clinical experts or better/more information in industry dossiers in order to ensure better knowledge.

Finally, the number of people responding to the marker has direct implications for the cost-effectiveness of treatment. If a small number of patients respond positively to the marker for example 5%, it means that the cost of using the test on 100 persons should be divided between the five patients who receive treatment. The costs of the diagnostic are important. If more people respond to the marker for example 50%, the total screening costs could be split between ten times more patients, making the use of the diagnostic tool much more cost-effective. In the later case, there are more people to treat and the costs of the diagnostics will be negligible.

5.3. EU cooperation in HTA

So far, the role and use of health technology assessments have varied considerably between the EU Member States. Through joint actions, the Commission supports cooperation between national bodies responsible for HTA (from EU Member States, EEA and accession countries). The Joint Action EUnetHTA⁴⁷, which also includes regional organisations and stakeholders’ representatives, aims to facilitate the exchange of information and to develop and test common methodological approaches to HTA.

To build on the results of EUnetHTA and strengthen further the cooperation between national HTA bodies, the Commission has established a permanent, voluntary HTA network at European level, in accordance with Article 15 of Directive 2011/24/EU on the application of patient rights in cross-border health care⁴⁸. EUnetHTA is a network of government-appointed organisations (from EU Member States, EEA and accession countries) and a large number of relevant regional agencies and not-for-profit organisations. The network is expected to produce joint assessments of health technologies which can be reused at national level and can ultimately create synergies and avoid duplication of efforts among bodies responsible for HTA throughout Europe. It should be noted that currently EU cooperation in HTA focuses on clinical issues, as economic, organisational, legal and ethical considerations are more addressed at national/regional level.

⁴⁷ EUnetHTA joint action: www.Eunetha.eu.

⁴⁸ Directive 2011/24/EU of the European Parliament and of the Council on the application of patient rights in cross-border health care, OJ L 88, 4.4.2011.

5.4. Pricing and reimbursement

The pricing and reimbursement systems in the Member States also play a role in the effective uptake of personalised medicine. These systems vary from Member State to Member State but across the board a trend is observed towards an increased uptake of so-called "managed entry" agreements whereby continued reimbursement is made conditional upon proven real-life effectiveness. Certain of schemes entail treatment cessation in treatment non-responder patients. Enhanced data collection in the frame of such schemes may further advance the evidence base underpinning personalised medicine. In addition, many Member States apply different procedures to determine, on the one hand, the price and reimbursement status of medicinal products, and, on the other hand, the inclusion of medical devices and in-vitro diagnostic tests in the health insurance system. Economic evaluation helps to assess the "value for money" of an intervention (i.e. the acceptability). In certain cases, budget impact analyses can also be requested to assess the affordability (predicated financial impact of introducing an intervention compared to the current situation).

The Belgian Health care Knowledge Centre published guidelines for economic evaluations and budget impact analysis to introduce methods to process reimbursement application for pharmaceuticals or devices⁴⁹.

Reference case methods for economic evaluations	
Literature review	Systematic review of up-to-date clinical and economic literature following methodological standards: reproducible search strategy, transparent selection criteria, critical appraisal.
Perspective of the evaluation	Costs: Health care payers (federal government + communities + patients). Outcomes: Society. For health-related quality of life, health states should be described by patients on a generic instrument. Health state valuations for these states should come from the general public.
Target population	Consistent with the clinical file. Relevant subgroups need to be defined. Post-hoc subgroup analyses only in case of statistical proof of difference in costs or baseline risk between the post-hoc subgroups.
Comparator	Economic relevant comparisons are performed on the efficiency frontier.
Analytic technique	Cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), choice should be justified.
Study design	Economic evaluation based as much as possible on data from head-to-head comparisons between the study product and the comparator.
Calculation of costs	Health care costs paid out of the health care budget, by the federal government, the communities and the patients.
Valuation of outcomes	Final endpoints. Cost-effectiveness analyses: life years gained for interventions with an impact on mortality. Cost-utility analyses: QALYs, with quality-of-life weights based on empirical data obtained with a generic quality-of-life instrument such as the EQ-5D for which public preference values exist.
Time horizon	The appropriate time horizon for the economic evaluation depends on the duration of the impact of the study intervention on relevant outcomes as compared to the comparator intervention.
Modelling	Based as much as possible on data from clinical studies comparing the study medication and the comparator, data from validated databases and/or data from literature. Model inputs and outputs consistent with existing data. Face validity checked. Clear presentation of structural hypotheses, assumptions and sources of information.
Handling uncertainty	Probabilistic sensitivity analyses for parameter uncertainty. Scenario analyses for analyses of methodological and structural uncertainty.

⁴⁹ https://kce.fgov.be/sites/default/files/page_documents/KCE_183C_economic_evaluations_second_edition_0.pdf

	Presentation of uncertainty around the incremental costs (IC), incremental effects (IE) and ICERs by means of confidence or credibility intervals. Results shown on the cost-effectiveness plane and cost-effectiveness acceptability curve.
Discount rate	3% on costs and 1.5% on outcomes.

As regards the costs, most authorities expect to receive information on direct health costs e.g. health services, medications, hospitalisation, etc. However, it is often recommended in the literature to use the societal viewpoint for the economic analysis, i.e. costs and outcomes for society as a whole should be valued. This would include costs borne outside the health care sector, such as productivity losses and travel expenses and *stricto sensu* also outcomes for patients' family.

Moreover, as regards genetic testing, reimbursement is not necessarily based on added value. Public laboratories might receive a standard budget for each sample examined, independent of the type of sample, the test or the work required to investigate it. According to a report from the OECD this practice may discourage low-volume, technically complex and expensive testing procedures and may drive the centralisation of testing services⁵⁰. Some stakeholders request increased coordination by national authorities responsible for pricing and reimbursement of medicinal products and medical devices or even the streamlining of national pricing and reimbursement procedures to enable personalised medicine technologies to reap their full potential⁵¹.

Challenges and opportunities:

- Challenges include adapting Health Technology Assessment methods to the needs of personalised medicine and developing and maintaining cross border sharing of expertise among HTA bodies.
- The benefits of personalised medicines are expected to offset their costs by efficiency gains. Rigorous evaluation offers the possibility to demonstrate the effectiveness of medical products and medical devices in comparison with other therapies. Successful uptake requires a *robust Health Technology Assessment*.
- The forthcoming establishment of a *permanent, HTA network at European level* will allow work models to be established for joint assessments of new health technologies. The information generated can be reused at national level, thereby reducing duplication of work between Member States.
- Challenges also include the fact that there are variable policies in EU as regards pricing and reimbursement⁵².

6. CONCLUSION

The development of personalised medicine through the use of -omics technologies offers new opportunities for the treatment of patients in the European Union. Through this approach, health care providers may be able to offer better targeted treatment, avoid medical errors and reduce adverse reactions to medicinal products.

⁵⁰ Pharmacogenetics, Opportunities and challenges for health innovation, OECD 2009, p. 109.

⁵¹ Europabio.

⁵² Priority Medicines for Europe and the World 2013 Update
http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/prioritymedicines_report_en.pdf

The current regulatory framework for pharmaceuticals offers a number of tools and procedures to ensure that medicines placed on the market have a high quality, safety and efficacy. These tools and procedures have been shown to work well for innovative products and orphan medicines, including therapies relevant to personalised medicine. The pharmaceutical legislation is flexible enough to address current needs and to authorise personalised medicines in a timely manner. The overall regulatory framework allows supporting the field with appropriate scientific guidelines and expert dialogue.

The new framework programme for research, Horizon 2020, and the ongoing revisions of important pieces of legislation address certain challenges identified in the development of these therapies, from basic research up to their placing on the market. The revision of the medical devices legislation will strengthen the oversight of *in vitro* diagnostics and introduce a better consultation process for companion diagnostics to assess patient eligibility for treatment with a specific medicinal product. The revision of the Clinical Trials Directive is expected to simplify the conduct of clinical trials and consequently facilitate the authorisation of research in therapies using personalised medicine. Moreover, a Health Technology Assessment taking into account the new technologies would provide a methodology for addressing the uptake of personalised medicine.

Personalised medicine is not a revolution but an evolution. Advances in science are expected in such a fast moving field. The European Commission will continue to monitor the developments of personalised medicine in the coming years and maintain a fruitful dialogue with stakeholders.

APPENDIX

RESEARCH CHALLENGES IN THE DEVELOPMENT OF PERSONALISED MEDICINE APPROACHES (IDENTIFIED IN THE CONFERENCE "EUROPEAN PERSPECTIVES IN PERSONALISED MEDICINE" IN MAY 2011 PRESENTED BY CONFERENCE SESSION)

The full report is available on: http://ec.europa.eu/research/health/policy-issues-personalised-medicine_en.html

Session 1: R&D – the basics

1. Make greater use of genome-wide-association studies and other ‘omics’ technologies to improve the understanding of molecular disease mechanisms, and by consequence the search for new drug targets.
2. Develop new animal models to test potential treatments for single-gene diseases.
3. Develop new treatments for single-gene diseases.
4. Explore drug targets identified through epigenomics.
5. Maintain Europe’s lead in the field of proteomics.
6. Develop new methods for validating biomarkers.
7. Support the commercialisation of new imaging technologies. Develop new imaging standards.
8. Make optimal use of mathematics, computer modelling and simulation to translate information from ‘-omics’ research into clinically relevant products and technologies.
9. Nurture multidisciplinary research bringing together clinicians and -omics specialists.
10. Support and develop standardised data collection and biobanking for disease cohorts.

Session 2: Biomarkers in personalised medicine

1. There is a need for high throughput screening platforms to identify biomarkers more quickly and cost-effectively; there is also a need for new validation techniques for candidate biomarkers.
2. Tools and methods need to be developed for the functional analysis of cells.
3. There is a need to standardise how specimens are collected within clinical trials, or for routine purposes and how data-sets are analysed.
4. European guidelines are needed for biomarker qualification and clinical validation.
5. Take advantage of new imaging technologies to understand biological mechanisms, including toxicity, at the molecular, whole organ, and whole body level.
6. Standard Operating Procedures (SOPs) are needed for tissue collection and analytical procedures.
7. A Europe-wide biobanking network is needed.
8. The issue of medicine-diagnostic co-development should be looked at.

9. Ethically compliant electronic patient records should be developed to inform biomarker research.

Session 3: The tests in humans – clinical aspects and clinical research

1. Develop Europe-wide biobanking.
2. Develop new trial methodologies including adaptive clinical trial design.
3. Promote the development and use of electronic patient records; use these electronic records to inform biomarker research.
4. Provide biomarker studies of generic medicines.
5. Consider the use of all types of biomarkers, not just molecular ones (also functional, imaging, etc.).
6. Many approaches (multi-modality) and not just medicines are needed in achieving personalised healthcare.
7. Standardise insurance requirements for clinical trials in Europe.

Session 4: Towards the market and patients – approval process

1. European clinical testing laboratories (both industry and hospital based) require clear regulatory standards and a stable reimbursement environment. Guidance is needed on which clinical endpoints are considered to deliver patient and societal value; guidance is also needed on innovative clinical trial designs and for the use of retrospectively generated data sets.
2. More investment is required in translational medicine, especially in applied molecular profiling and imaging technologies.
3. A uniform quality framework and delivery infrastructure that maximises patient access is needed for companion diagnostic testing in Europe.
4. More unified and coordinated accreditation procedures should be established for European clinical testing laboratories.
5. There should be a more focused and coordinated effort to use patient registries, patient biological samples, and patient outcome data in a targeted personalised medicine development programme with results published in a timely manner.

Session 5: Uptake in healthcare – post-approval process

1. Research should be undertaken to better measure patient outcomes in the context of personalised medicines.
2. Discussions between medicine regulators, health technology bodies and industry about measuring efficacy/effectiveness should continue.
3. The regulation of the components of personalised medicine (e.g., medicines and diagnostics) should be coordinated. A central role for the EMA was mentioned as a possible solution.
4. Research into viable business models to help support the introduction of personalised medicine and related technologies should be initiated.

Session 6: In the clinic – practitioner and patient perspectives

1. Explore what the barriers are to achieve clinical added value by the introduction of personalised medicine approaches.
2. Provide more education and training to clinicians in the use of the new diagnostics, and make sure the required facilities are easily available.
3. Make better use of the biomarkers that we already have before introducing new ones.
4. Get all stakeholders to collaborate in translating research into clinical practice, with an emphasis on patient participation.
5. Explore the social consequences, e.g. insurance and employment, for patients who overcome a serious or debilitating disease. Are there mechanisms for reintegrating them into society?